



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: C07D 213/79, A61K 31/435, A61P 29/00, A61P 37/00, C07D 401/12, C07D 403/12		A1	(11) International Publication Number: WO 00/32575 (43) International Publication Date: 08 June 2000 (08.06.2000)
<p>(21) International Application Number: PCT/GB99/03986</p> <p>(22) International Filing Date: 29 November 1999 (29.11.1999)</p> <p>(30) Priority Data: 9826174.6 30 November 1998 (30.11.1998) GB</p> <p>(60) Parent Application or Grant CELLTECH THERAPEUTICS LIMITED [/]; O. PORTER, John, Robert [/]; O. HEAD, John, Clifford [/]; O. WARRELOW, Graham, John [/]; O. ARCHIBALD, Sarah, Catherine [/]; O. PORTER, John, Robert [/]; O. HEAD, John, Clifford [/]; O. WARRELOW, Graham, John [/]; O. ARCHIBALD, Sarah, Catherine [/]; O. MERCER, Christopher, Paul ; ()</p>		Published	
<p>(54) Title: 'beta'-ALANINE DERIVATIVES AS 'alpha'4 INTEGRIN INHIBITORS (54) Titre: DÉRIVES DE 'beta'-ALANINE COMME INHIBITEURS DES 'alpha'4 INTÉGRINES</p> <p>(57) Abstract Alkanoic acid derivatives of formula (1) are described: $Ar_1\zeta(Alk\alpha\zeta)\zeta L_1\zeta Ar_2\zeta CH(R_1\zeta)C(R\alpha\zeta)R$ wherein $Ar_1\zeta$ is an optionally substituted aromatic or heteroaromatic group; $L_1\zeta$ is a covalent bond or a linker atom or group; $Ar_2\zeta$ is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group; R is a carboxylic acid ($-CO\zeta_2H$) or a derivative thereof; and the salts, solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of 'alpha'4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.</p> <p>(57) Abrégé La présente invention concerne des dérivés d'acides alcanoïques représentés par la formule (1) telle que $Ar_1\zeta(Alk\alpha\zeta)\zeta L_1\zeta Ar_2\zeta CH(R_1\zeta)C(R\alpha\zeta)R$, ou l'un des sels, solvates, hydrates et N-oxydes de ces dérivés. $Ar_1\zeta$ est un groupe aromatique hétéroaromatique éventuellement substitué. $L_1\zeta$ est une liaison par covalence ou un groupe ou atome de liaison. $Ar_2\zeta$ est un groupe phényle éventuellement substitué ou un groupe hétéroarylène azoté à six chaînons. R est acide carboxylique ($-CO\zeta_2H$) ou l'un de ses dérivés. Ces composés, qui permettent de bloquer la liaison des 'alpha'4 intégrines à leurs ligands, conviennent pour la prophylaxie et le traitement des troubles d'origine immunitaire ou inflammatoire.</p>			

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 : C07D 213/79, A61K 31/435, A61P 37/00, 29/00, C07D 401/12, 403/12		A1	(11) International Publication Number: WO 00/32575 (43) International Publication Date: 8 June 2000 (08.06.00)
(21) International Application Number: PCT/GB99/03986 (22) International Filing Date: 29 November 1999 (29.11.99) (30) Priority Data: 9826174.6 30 November 1998 (30.11.98) GB		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(71) Applicant (for all designated States except US): CELLTECH THERAPEUTICS LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): PORTER, John, Robert [GB/GB]; 5 Farm Place, Henton, Chinnor, Oxfordshire OX9 4AD (GB). HEAD, John, Clifford [GB/GB]; 4 Dorchester Close, Maidenhead, Berkshire SL6 6RX (GB). WARRELOW, Graham, John [GB/GB]; Oakside, 4 Wieland Road, Northwood, Middlesex HA6 2QU (GB). ARCHIBALD, Sarah, Catherine [GB/GB]; 5 College Glen, Maidenhead, Berkshire SL6 6BL (GB). (74) Agent: MERCER, Christopher, Paul; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).		Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: β-ALANINE DERIVATIVES AS $\alpha 4$ INTEGRIN INHIBITORS			
(57) Abstract			
<p>Alkanoic acid derivatives of formula (I) are described: $Ar^1(Alk^a)_nL^1Ar^2CH(R^1)C(R^a)(R^4)R$ wherein Ar^1 is an optionally substituted aromatic or heteroaromatic group; L^1 is a covalent bond or a linker atom or group; Ar^2 is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group; R is a carboxylic acid ($-CO_2H$) or a derivative thereof; and the salts, solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of $\alpha 4$ integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.</p>			

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	IS	Iceland	UG	Uganda
BY	Belarus	IT	Italy	MW	Malawi	US	United States of America
CA	Canada	JP	Japan	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	KE	Kenya	NE	Niger	VN	Viet Nam
CG	Congo	KG	Kyrgyzstan	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KP	Democratic People's Republic of Korea	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KR	Republic of Korea	NZ	New Zealand		
CM	Cameroon	KZ	Kazakhstan	PL	Poland		
CN	China	LC	Saint Lucia	PT	Portugal		
CU	Cuba	LI	Liechtenstein	RO	Romania		
CZ	Czech Republic	LK	Sri Lanka	RU	Russian Federation		
DE	Germany	LR	Liberia	SD	Sudan		
DK	Denmark			SE	Sweden		
EE	Estonia			SG	Singapore		

Description

5

10

15

20

25

30

35

40

45

50

55

5

 β -ALANINE DERIVATIVES AS $\alpha 4$ INTEGRIN INHIBITORS

10 This invention relates to a series of alcanoic acid derivatives, to processes for their preparation, and to their use in medicine.

5 Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T A. *Nature*, 346, 425, (1990); Springer, T. A. *Cell* 76,
15 10, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

20 The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is
25 believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. *Current Topics in Microbiology and Immunology*, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha 4\beta 1$
30 20 consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not
35 25 all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised
40 [Sonnenberg, A. *ibid*].

30 The importance of cell adhesion molecules in human leukocyte function
45 has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. *et al* *J. Exp. Med.* 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

50

55

5

2

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

10

The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al* Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al* J. Immunol. 157, 4094, (1996)]. A number of monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

20

One particular integrin subgroup of interest involves the $\alpha 4$ chain which can pair with two different beta chains $\beta 1$ and $\beta 7$ [Sonnenberg, A. *ibid*]. The $\alpha 4\beta 1$ pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. $\alpha 4\beta 1$ binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1) frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed that the interaction between $\alpha 4\beta 1$ and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

30 The integrin generated by the pairing of $\alpha 4$ and $\beta 7$ has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like $\alpha 4\beta 1$, binds to VCAM-1 and fibronectin. In addition, $\alpha 4\beta 7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between $\alpha 4\beta 7$ and MAdCAM-1 may also be important at sites of

45

50

55

5

3

inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

10

Regions of the peptide sequence recognised by $\alpha 4\beta 1$ and $\alpha 4\beta 7$ when they bind to their ligands have been identified. $\alpha 4\beta 1$ seems to recognise LDV, IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha 4\beta 7$ recognises a LDT sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719, (1996)]. There have been several reports of inhibitors of these interactions being designed from modifications of these short peptide sequences [Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N. Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol. 158, 1710, (1997)]. It has also been reported that a short peptide sequence derived from the $\alpha 4\beta 1$ binding site in fibronectin can inhibit a contact hypersensitivity reaction in a trinitrochlorobenzene sensitised mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

15

20

25

Since the alpha 4 subgroup of integrins are predominantly expressed on leukocytes their inhibition can be expected to be beneficial in a number of immune or inflammatory disease states. However, because of the ubiquitous distribution and wide range of functions performed by other members of the integrin family it is very important to be able to identify selective inhibitors of the alpha 4 subgroup.

30

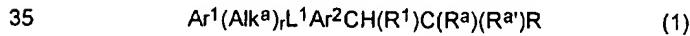
40

45

We have now found a group of compounds which are potent and selective inhibitors of $\alpha 4$ integrins. Members of the group are able to inhibit $\alpha 4$ integrins such as $\alpha 4\beta 1$ and/or $\alpha 4\beta 7$ at concentrations at which they generally have no or minimal inhibitory action on α integrins of other subgroups. The compounds are thus of use in medicine, for example in the prophylaxis and treatment of immune or inflammatory disorders as described hereinafter.

50

Thus according to one aspect of the invention we provide a compound of formula (1):



55

wherein

Ar¹ is an optionally substituted aromatic or heteroaromatic group;

10 L¹ is a covalent bond or a linker atom or group selected from -CON(R²)- [where R² is a hydrogen atom or a C₁₋₃alkyl group], -SO₂N(R²)-, -C(O)O-, -N(R²)- or -O-;

5 Ar² is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group;

15 R¹ is a group selected from -NHCOR³ [where R³ is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group], -NHSO₂R³, -NHR³, -NHC(O)OR³, -NHCSR³, -NHCOR³(R^{3a}) [where R^{3a} is a hydrogen atom or a group R³ and R³ and R^{3a} are the same or different], -NHSO₂N(R³)(R^{3a}), -NHCSN(R³)(R^{3a}), -CON(R³)(R^{3a}) or -CSN(R³)(R^{3a});

20 25 R^a and R^{a'} which may be the same or different is each independently selected from a hydrogen or halogen atom or an optionally substituted straight or branched alkyl, alkenyl or alkynyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, or -(Alk^b)_mR^b group (in which Alk^b is a C₁₋₃alkylene chain, m is zero or the integer 1 and R^b is a -OH, -SH, -NO₂, -CN, -CO₂H, -CO₂R^c, 30 35 40 (where R^c is an optionally substituted straight or branched C₁₋₆alkyl group), -SO₃H, -SOR^c, -SO₂R^c, -SO₃R^c, -OCO₂R^c, -C(O)H, -C(O)R^c, -OC(O)R^c, -C(S)R^c, -NR^dR^e [where R^d and R^e which may be the same or different is each a hydrogen atom or an optionally substituted straight or branched alkyl group], -C(O)N(R^d)(R^e), -OC(O)N(R^d)(R^e), -N(R^d)C(O)R^e, -CSN(R^d)(R^e), -N(R)^dC(S)R^e, -SO₂N(R^d)(R^e), -N(R^d)SO₂R^e, -N(R^d)CON(R^e)(R^f) [where R^f is a hydrogen atom or an optionally substituted straight or branched alkyl group], -N(R^d)C(S)N(R^e)(R^f) or -N(R^d)SO₂N(R^e)(R^f) group].

Alk^a is an optionally substituted aliphatic or heteroaliphatic chain;

30 r is zero or the integer 1;

45 R is a carboxylic acid (-CO₂H) or a derivative thereof; and the salts, solvates, hydrates and N-oxides thereof.

It will be appreciated that compounds of formula (1) may have one or more 35 chiral centres, and exist as enantiomers or diastereomers. The invention is 50 to be understood to extend to all such enantiomers, diastereomers and

mixtures thereof, including racemates. Formula (1) and the formulae hereinafter are intended to represent all individual isomers and mixtures thereof, unless stated or shown otherwise.

10

15

20

25

30

35

40

45

50

55

5 In the compounds of the invention as represented by formula (1) and the more detailed description hereinafter certain of the general terms used in relation to substituents are to be understood to include the following atoms or groups unless specified otherwise.

10 Thus as used herein the term "straight or branched alkyl", whether present as a group or part of a group includes straight or branched C₁-6alkyl groups, for example C₁-4alkyl groups such as methyl, ethyl, n-propyl, i-propyl or t-butyl groups. Similarly, the terms "straight or branched alkenyl" or "straight or branched alkynyl" are intended to mean C₂-6alkenyl or C₂-6alkynyl groups such as C₂-4alkenyl or C₂-4alkynyl groups.

15 The term "halogen atom" is intended to include fluorine, chlorine, bromine or iodine atoms.

20 The term "straight or branched haloalkyl" is intended to include the alkyl groups just mentioned substituted by one, two or three of the halogen atoms just described. Particular examples of such groups include -CF₃, -CCl₃, -CHF₂, -CHCl₂, -CH₂F, and -CH₂Cl groups.

25 The term "straight or branched alkoxy" as used herein is intended to include straight or branched C₁-6alkoxy e.g. C₁-4alkoxy such as methoxy, ethoxy, n-propoxy, i-propoxy and t-butoxy. "Haloalkoxy" as used herein includes any of those alkoxy groups substituted by one, two or three halogen atoms as described above. Particular examples include -OCF₃, -OCCl₃, -OCHF₂, -OCHCl₂, -OCH₂F and -OCH₂Cl groups.

30 As used herein the term "straight or branched alkylthio" is intended to include straight or branched C₁-6alkylthio, e.g. C₁-4alkylthio such as methylthio or ethylthio groups.

35

40

45

50

55

10 In the compounds of formula (1), derivatives of the carboxylic acid group R include carboxylic acid esters and amides. Particular esters and amides include -CO₂Alk¹ and -CONR⁵R⁶ groups as described herein.

15 5 When Alk^a is present in compounds of formula (1) as an optionally substituted aliphatic or heteroaliphatic chain it may be for example any divalent chain corresponding to the below-mentioned aliphatic or heteroaliphatic groups described for R³.

20 10 Aromatic groups represented by the group Ar¹ in compounds of the invention include for example monocyclic or bicyclic fused ring C₆-12 aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

25 15 Heteroaromatic groups represented by the group Ar¹ in the compounds of formula (1) include for example C₁₋₉ heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups.

30 20 Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example eight- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

35 40 Particular examples of heteroaromatic groups of these types include pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆alkylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, benzothienyl, benzotriazolyl, indolyl, indolinyl, isoindolyl, indazolinyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, 45 35 benzopyranyl, [3,4-dihydro]benzopyranyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]-

10 pyridyl, quinoliny, isoquinoliny, tetrazolyl, 5,6,7,8-tetrahydroquinoliny, 5,6,7,8-tetrahydroisoquinoliny, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

15 5 Each aromatic or heteroaromatic group represented by the group Ar¹ may be optionally substituted on any available carbon or, when present, nitrogen atom. One, two, three or more of the same or different substituents may be present and each substituent may be selected for example from an atom or group -L²(Alk)_tL³(R⁴)_u in which L² and L³, which 10 may be the same or different, is each a covalent bond or a linker atom or group, t is zero or the integer 1, u is an integer 1, 2 or 3, Alk is an aliphatic or heteroaliphatic chain and R⁴ is a hydrogen or halogen atom or a group selected from C₁₋₆alkyl, -OR⁵ [where R⁵ is a hydrogen atom or an optionally substituted C₁₋₆alkyl group], -SR⁵, -NR⁵R⁶ [where R⁶ is as just 15 defined for R⁵ and may be the same or different], -NO₂, -CN, -CO₂R⁵, -SO₃H, -SO₃R⁵, -SOR⁵, -SO₂R⁵, -OCO₂R⁵, -CONR⁵R⁶, -OCONR⁵R⁶, -CSNR⁵R⁶, -COR⁵, -OCOR⁵, -N(R⁵)COR⁶, -N(R⁵)CSR⁶, -SO₂N(R⁵)(R⁶), -N(R⁵)SO₂R⁶, N(R⁵)CON(R⁶)(R⁷) [where R⁷ is a hydrogen atom or an optionally substituted C₁₋₆alkyl group], -N(R⁵)CSN(R⁶)(R⁷) or 20 -N(R⁵)SO₂N(R⁶)(R⁷), provided that when t is zero and each of L² and L³ is a covalent bond then u is the integer 1 and R⁴ is other than a hydrogen atom

35 35 When L² and/or L³ is present in these substituents as a linker atom or 40 group it may be any divalent linking atom or group. Particular examples include -O- or -S- atoms or -C(O)-, -C(O)O-, -OC(O)-, -C(S)-, -S(O)-, -S(O)₂-, -N(R⁸)- [where R⁸ is a hydrogen atom or an optionally substituted C₁₋₆alkyl group], -CON(R⁸)-, -OC(O)N(R⁸)-, -CSN(R⁸)-, -N(R⁸)CO-, -N(R⁸)C(O)O-, -N(R⁸)CS-, -S(O)₂N(R⁸)-, -N(R⁸)S(O)₂-, 45 30 -N(R⁸)CON(R⁸)-, -N(R⁸)CSN(R⁸)-, or -N(R⁸)SO₂N(R⁸)- groups. Where the linker group contains two R⁸ substituents, these may be the same or different.

50 55 When R^c, R^d, R^e, R^f, R⁴, R⁵, R⁶, R⁷ and/or R⁸ is present as a C₁₋₆alkyl group it may be a straight or branched C₁₋₆alkyl group, e.g. a C₁₋₃alkyl group such as a methyl or ethyl group. Optional substituents which may be

10

present on such groups include for example one, two or three substituents which may be the same or different selected from halogen atoms, for example fluorine, chlorine, bromine or iodine atoms, or hydroxy or C₁-6alkoxy e.g. methoxy or ethoxy groups.

15

5

When Alk is present as an aliphatic or heteroaliphatic chain it may be for example any divalent chain corresponding to the below-mentioned aliphatic or heteroaliphatic group described for R³.

20

10 Halogen atoms represented by R⁴ in the optional Ar¹ substituents include fluorine, chlorine, bromine, or iodine atoms.

25

Examples of the substituents represented by -L²(Alk)₁L³(R⁴)₀ when present in Ar¹ groups in compounds of the invention include atoms or groups -L²AlkL³R⁴, -L²AlkR⁴, -L²R⁴ and -AlkR⁴ wherein L², Alk, L³ and R⁴ are as defined above. Particular examples of such substituents include -L²CH₂L³R⁴, -L²CH(CH₃)L³R⁴, -L²CH₂(CH₂)₂L³R⁴, -L²CH₂R⁴, -L²CH(CH₃)R⁴, -L²(CH₂)₂R⁴, -CH₂R⁴, -CH(CH₃)R⁴, -(CH₂)₂R⁴ and -R⁴ groups.

30

20

Thus Ar¹ in compounds of the invention may be optionally substituted for example by one, two, three or more halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, and/or C₁-6alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C₁-6alkylamino, e.g. methylamino or ethylamino, C₁-6hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or -C(OH)(CF₃)₂, carboxyC₁-6alkyl, e.g. carboxyethyl, C₁-6alkylthio e.g. methylthio or ethylthio, carboxyC₁-6alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁-6alkoxy, e.g. methoxy or ethoxy, optionally substituted C₆-12arylC₁-6alkyloxy e.g. benzyloxy, hydroxyC₁-6alkoxy, e.g. 2-hydroxyethoxy, haloC₁-6alkyl, e.g. -CF₃, -CHF₂, CH₂F, haloC₁-6alkoxy, e.g. -OCF₃, -OCHF₂, -OCH₂F, C₁-6alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁-6alkyl, e.g. aminomethyl or aminoethyl, C₁-6dialkylamino, e.g. dimethylamino or diethylamino, C₁-6alkylaminoC₁-6alkyl, e.g. ethylaminoethyl, C₁-6 dialkylaminoC₁-6alkyl, e.g. diethylaminoethyl, aminoC₁-6alkoxy, e.g. aminoethoxy, hydroxyC₁-6alkylamino e.g. hydroxyethylamino or hydroxypropylamino, C₁-6alkylaminoC₁-

50

55

10

When the group R³ is present in compounds of formula (1) as an optionally substituted aliphatic group it may be an optionally substituted C₁₋₁₀ aliphatic group. Particular examples include optionally substituted straight or branched chain C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl groups.

15

Heteroaliphatic groups represented by the group R³ include the aliphatic groups just described but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L⁴ where L⁴ is as defined above for L² when L² is a linker atom or group. Each L⁴ atom or group may interrupt the aliphatic group, or may be positioned at its terminal carbon atom to connect the group to an adjoining atom or group.

20

Particular examples of aliphatic groups represented by the group R³ include optionally substituted -CH₃, -CH₂CH₃, -CH(CH₃)₂, -(CH₂)₂CH₃, -CH(CH₃)CH₃, -(CH₂)₃CH₃, -CH(CH₃)CH₂CH₃, -CH₂CH(CH₃)₂, -C(CH₃)₃, -(CH₂)₄CH₃, -(CH₂)₅CH₃, -CHCH₂, -CHCHCH₃, -CH₂CHCH₂, -CHCHCH₂CH₃, -CH₂CHCHCH₃, -(CH₂)₂CHCH₂, -CCH, -CCCH₃, -CH₂CCH, -CCCH₂CH₃, -CH₂CCCH₃, or -(CH₂)₂CCH groups. Where appropriate each of said groups may be optionally interrupted by one or two atoms and/or groups L⁴ to form an optionally substituted heteroaliphatic group. Particular examples include optionally substituted -L⁴CH₃, -CH₂L⁴CH₃, -L⁴CH₂CH₃, -CH₂L⁴CH₂CH₃, -(CH₂)₂L⁴CH₃, -L⁴(CH₂)₃CH₃ and -(CH₂)₂L⁴CH₂CH₃ groups.

30

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by R³ include one, two, three or more substituents where each substituent may be the same or different and is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxy, C₁₋₆alkoxy, e.g. methoxy or ethoxy, thiol, C₁₋₆alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include -NHR⁹ and -N(R⁹)₂ groups where R⁹ is an optionally substituted straight or branched C₁₋₆alkyl group as defined above for R⁴. Where two R⁹ groups are present these may be the same or different. Particular examples of substituted groups represented by R³ include those

45

50

55

5

11

10

specific groups just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example groups of the type -CHCF₃, -CH(CF₃)₂, -CH₂CH₂CF₃, -CH₂CH(CF₃)₂ and -C(CF₃)₂CH₃.

15

5 Optionally substituted cycloaliphatic groups represented by the group R³ in compounds of the invention include optionally substituted C₃-10 cycloaliphatic groups. Particular examples include optionally substituted C₃-10 cycloalkyl, e.g. C₃-7 cycloalkyl or C₃-10 cycloalkenyl, e.g. C₃-7 cycloalkenyl groups.

20

10 Optionally substituted heterocycloaliphatic groups represented by the group R³ include optionally substituted C₃-10 heterocycloaliphatic groups. Particular examples include optionally substituted C₃-10 heterocycloalkyl, e.g. C₃-7 heterocycloalkyl, or C₃-10 heterocycloalkenyl, e.g. C₃-7 heterocycloalkenyl groups, each of said groups containing one, two, three or four heteroatoms or heteroatom-containing groups L⁴ as defined above.

25

20 Optionally substituted polycycloaliphatic groups represented by the group R³ include optionally substituted C₇-10 bi- or tricycloalkyl or C₇-10 bi- or tricycloalkenyl groups. Optionally substituted heteropolycycloaliphatic groups represented by the group R³ include the optionally substituted polycycloalkyl groups just described, but with each group additionally containing one, two, three or four L⁴ atoms or groups.

30

35 25 Particular examples of cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and heteropolycycloaliphatic groups represented by the group R³ include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, tetrahydrofuranyl, 40 30 pyrrolidine, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholinyl, morpholinone, 1,4-dithianyl, 45 35 thiomorpholinyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, e.g. o-

50

55

5

12

or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5,-oxadiazinyl groups.

10

The optional substituents which may be present on the cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or heteropolycycloaliphatic groups represented by the group R³ include one, two, three or more substituents each selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C₁-alkyl, e.g. methyl or ethyl, haloC₁-alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, optionally substituted by hydroxyl, e.g. -C(OH)(CF₃)₂, hydroxyl, C₁-alkoxy, e.g. methoxy or ethoxy, haloC₁-alkoxy, e.g. halomethoxy or haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C₁-alkylthio e.g. methylthio or ethylthio, or -(Alk²)_vR¹⁰ groups in which Alk² is a straight or branched C₁-3 alkylene chain, v is zero or an integer 1 and R¹⁰ is a -OH, -SH, -N(R¹¹)₂, -CN, -CO₂R¹¹, -NO₂, -CON(R¹¹)₂, -CSN(R¹¹)₂, -OC(O)N(R¹¹)₂, -C(O)H, -COR¹¹, -OCO₂R¹¹, -OC(O)R¹¹, -C(S)R¹¹, -CSN(R¹¹)₂, -N(R¹¹)COR¹¹, -N(R¹¹)CSR¹¹, -SO₃H, -SOR¹¹, -SO₂R¹¹, -SO₃R¹¹, -SO₂N(R¹¹)₂, -N(R¹¹)SO₂R¹¹, -N(R¹¹)CON(R¹¹)₂, -N(R¹¹)CSN(R¹¹)₂ or -N(R¹¹)SO₂N(R¹¹)₂ [in which R¹¹ is an atom or group as defined herein for R⁸ or an optionally substituted cycloaliphatic or heterocycloaliphatic group as previously defined for R³] aromatic or heteroaromatic group. Where two R¹¹ atoms or groups are present in these substituents these may be the same or different.

20

25 Additionally, when the group R³ is a heterocycloaliphatic group containing one or more nitrogen atoms each nitrogen atom may be optionally substituted by a group -(L⁵)_p(Alk³)_qR¹² in which L⁵ is -C(O)-, -C(O)O-, -C(S)-, -S(O)-, -S(O)₂-, -CON(R¹¹)-, -CSN(R¹¹)-, -SON(R¹¹)- or SO₂N(R¹¹)-; p is zero or an integer 1; Alk³ is an optionally substituted aliphatic or heteroaliphatic chain; q is zero or an integer 1; and R¹² is a hydrogen atom or an optionally substituted cycloaliphatic, heterocycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group.

30

30 35 Optionally substituted aliphatic or heteroaliphatic chains represented by Alk³ include those optionally substituted chains described above for R³.

45

50

55

10

groups [where R^{15} is a hydrogen atom or C_{1-6} alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R^{11} or R^{14} groups are present in one of the above substituents, the R^{11} or R^{14} groups may be the same or different.

15

5

When in the group $-Alk^4(R^{13a})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13a} may be present on any suitable carbon atom in $-Alk^4$. Where more than one R^{13a} substituent is present these may be the same or different and may be present on the same or different atom in $-Alk^4$. Clearly, when m is zero and no substituent R^{13a} is present the alkylene, alkenylene or alkynylene chain represented by Alk^4 becomes an alkyl, alkenyl or alkynyl group.

20

10

When R^{13a} is a substituted amino group it may be for example a group $-NHR^{14}$ [where R^{14} is as defined above] or a group $-N(R^{14})_2$ wherein each R^{14} group is the same or different.

25

30

15

When R^{13a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

20

When R^{13a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^{14}$ or a $-SR^{14}$ or $-SC(=NH)NH_2$ group respectively.

35

25

Esterified carboxyl groups represented by the group R^{13a} include groups of formula $-CO_2Alk^1$ wherein Alk^1 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *s*-butyl or *t*-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted phenoxyethyl, phenoxyethyl, 1-naphthoxyethyl, or 2-naphthoxyethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxyethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aroyloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxy-

40

45

30

40

35

50

55

5

15

propyl group. Optional substituents present on the Alk¹ group include R^{13a} substituents described above.

10

When Alk⁴ is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or -S(O)-, -S(O)₂- or -N(R¹²)- groups.

15

10

20

Aryl or heteroaryl groups represented by the groups R^{13a} or R¹⁴ include mono- or bicyclic optionally substituted C₆₋₁₂ aromatic or C₁₋₉ heteroaromatic groups as described above for the group Ar¹. The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

25

30

When -NHet¹ or -Het² forms part of a substituent R¹³ each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally Het² may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ or -Het² include those substituents as described for R³ cycloaliphatic groups above.

35

25

40

Particularly useful atoms or groups represented by R¹³ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thiazolyl, thienyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrrolidinyl, or piperidinyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyloxy, phenylthio e.g. 3,5-dimethoxyphenylthio, or pyridylthio, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy,

50

55

5

16

10

haloC₁₋₆alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino, ethylamino or propylamino, optionally substituted C₆₋₁₂arylC₁₋₆alkylamino e.g. benzylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. 5 dimethylamino or diethylamino, aminoC₁₋₆alkylamino e.g. aminomethylamino, aminoethylamino or aminopropylamino, optionally substituted Het¹NC₁₋₆alkylamino e.g. morpholinopropylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. 10 methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, diisopropylaminoethoxy, or dimethylaminopropoxy, hydroxyC₁₋₆alkylamino, e.g. hydroxyethylamino or hydroxypropylamino, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, 15 cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁵ [where Alk⁵ is as defined above], C₁₋₆ alkanoyl e.g. acetyl, 20 optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), C₁₋₆alkylsulphanyl, e.g. methylsulphanyl, ethylsulphanyl or propylsulphanyl, C₁₋₆alkylsulphonyl, e.g. 25 methylsulphonyl, ethylsulphonyl or propylsulphonyl, optionally substituted phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, 30 C₆₋₁₀arylsulphonyl e.g. phenylsulphonyl, dichlorophenylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylamino- 35 sulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, optionally substituted phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, 40 e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylamino- 45 carbonyl, e.g. aminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylamino- carbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminoarbonylamino, e.g. methylaminocarbonylamino or ethylamino- 50 carbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocarbonylamino, C₁₋₆alkyl-aminothiocarbonylamino, e.g. methylaminothiocarbonylamino or ethylaminothiocarbonylamino, C₁₋₆dialkylaminothiocarbonyl- 55 amino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonylamino, C₁₋₆alkylaminothiocarbonylC₁₋₆alkyl-amino, e.g. ethylaminothio-

55

5

17

10

carbonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkyl-amino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoyl-amino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyloxy-carbonylaminoethyl, thiobenzyl, pyridylmethylthio or thiazolylmethylthio groups.

20 20 Where desired, two R¹³ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as methylenedioxy or ethylenedioxy.

35 25 It will be appreciated that where two or more R¹³ substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the aromatic or heteroaromatic group represented by R³.

40 30 Nitrogen-containing six-membered heteroarylene groups represented by the group Ar² in compounds of formula (1) include pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl and triazinyl groups. Each group may be attached to the remainder of the molecule through any available ring carbon atom.

45 35 The phenylene and nitrogen-containing heteroarylene groups represented by Ar² may be optionally substituted by one or two substituents selected

50

55

5

18

from the atoms or groups $-L^2(Alk)_1L^3(R^4)_u$ described herein. Where two of these atoms or groups are present they may be the same or different.

10

5 The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

15

10 Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

20

25 Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

30

30 Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

35

35 In the compounds according to the invention the group Ar^1 is preferably an optionally substituted phenyl or monocyclic heteroaromatic group. Particularly useful groups of this type are optionally substituted five- or six-membered heteroaromatic groups as described previously, especially five- or six-membered heteroaromatic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen atoms. Nitrogen-containing groups are especially useful, particularly pyridyl or pyrimidinyl groups. Particularly useful substituents present on Ar^1 groups include halogen atoms or alkyl, $-OR^5$, $-SR^5$, $-NR^5R^6$, $-CO_2H$, $-CO_2CH_3$, NO_2 or $-CN$ groups as described above in relation to the compounds of formula (1).

40

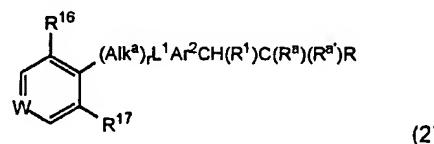
45

50

55

10 In one group of compounds of formula (1) for example R^a and R^{a'} is each a hydrogen atom, r is zero and R is a carboxylic acid (-CO₂H).

15 5 A particularly useful group of compounds according to the invention has the formula (2):



25 10 wherein -W= is -CH= or -N=;

25 15 R¹⁶ and R¹⁷, which may be the same or different is each a hydrogen atom or an atom or group -L²(Alk)_tL³(R⁴)_u in which L², Alk, t, L³, R⁴ and u are as defined previously;

25 20 Alk^a, L¹, R¹, Ar², R^a and R are as defined for formula (1);

25 25 and the salts, solvates, hydrates and N-oxides thereof.

30 -W= in compounds of formula (2) is preferably -N=.

35 20 R¹⁶ and R¹⁷ in compounds of formula (2) is each preferably as particularly described above for compounds of formula (1), other than a hydrogen atom. Particularly useful R¹⁶ and R¹⁷ substituents include halogen atoms, especially fluorine or chlorine atoms, or methyl, halomethyl, especially -CF₃, -CHF₂ or -CH₂F, methoxy or halomethoxy, especially -OCF₃, -OCHF₂ or -OCH₂F groups. Especially preferred R¹⁶ and R¹⁷ substituents are chlorine atoms.

40 25 R in the compounds of formulae (1) and (2) is preferably a -CO₂H group.

45 30 In one preferred group of compounds of formulae (1) and (2) r is preferably zero and L¹ is preferably -CON(R²). An especially useful L¹ group is -CONH-.

5

20

10

In another preferred group of compounds of formulae (1) and (2) r is preferably the integer 1 and Alk^a is preferably an aliphatic chain, particularly a C_{1-6} alkyl chain, most especially a $-\text{CH}_2-$ group. In this group of compounds L^1 is preferably an $-\text{O}-$ atom.

5

15

R^a in compounds of formulae (1) and (2) is preferably a hydrogen atom or an $-\text{OH}$ group. An especially preferred R^a atom in compounds of formula (1) and (2) is a hydrogen atom.

20

10 The group Ar^2 in compounds of formulae (1) and (2) is preferably an optionally substituted phenylene group. Particularly useful groups include optionally substituted 1,4-phenylene groups.

25

15 Particularly useful R^1 groups in compounds of the invention are those wherein R^1 is a $-\text{NHCOR}^3$ or $-\text{NHR}^3$ group.

30

In general in compounds of formulae (1) and (2) the group R^3 may especially be an optionally substituted cycloaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group as defined herein. Particularly useful 20 groups of this type include optionally substituted C_{5-7} cycloaliphatic, especially optionally substituted cyclopentyl and cyclohexyl, optionally substituted C_{5-7} heterocycloaliphatic, especially optionally substituted pyrrolidinyl or thiazolidinyl, optionally substituted phenyl and optionally substituted C_{5-7} heteroaromatic, especially optionally substituted pyridyl 35 and 1,3,5-triazinyl groups.

40

Optional substituents on these groups include in particular R^{13} atoms or groups where R^3 is an aromatic or heteroaromatic group. Particularly useful R^{13} atoms or groups include a halogen atom, especially fluorine or 30 chlorine, C_{1-6} alkoxy, especially methoxy, optionally substituted phenoxy and phenylthio, especially phenoxy and 2,5-dimethoxyphenylthio, hydroxy C_{1-6} alkylamino, especially hydroxyethylamino, C_{1-6} alkylsulphiny 45 especially propylsulphiny, C_{1-6} alkylsulphonyl, especially propylsulphonyl or C_{6-10} arylsulphonyl, especially phenylsulphonyl or dichlorophenylsulphonyl.

35

50

55

Where R³ is a nitrogen-containing heterocycloaliphatic group such as a pyrrolidinyl or thiazolidinyl group optional substituents include in particular -(L⁵)_p(Alk³)_qR¹² groups as described earlier.

10 5 Particularly useful -(L⁵)_p(Alk³)_qR¹² groups include those in which p is the integer 1 and L⁵ is a -CO- or -S(O)₂- group. When L⁵ is -CO- Alk³ is preferably present (i.e. q is preferably an integer 1) and in particular is a -CH₂-chain. R¹² in groups of this type is preferably a hydrogen atom. When L⁵ is -S(O)₂- q is preferably zero. Compounds of this type in which 15 10 R¹² is an optionally substituted aromatic or heteroaromatic group, especially an optionally substituted phenyl, e.g. dichlorophenyl, pyridyl or 20 imidazolyl group are particularly preferred.

Particularly useful compounds of the invention include:

25 15 3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-{(4-[2-hydroxyethyl]-
amino]-6-methoxy-1,3,5-triazin-2-yl)amine}propanoic acid;
3-{(3,5-Dichloroisonicotinoyl)amino]-3-{4-[(3,5-dichloroisonicotinoyl)-
amino]phenyl}propanoic acid;
3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-{(2,6-
30 20 dimethoxybenzoyl)amino}propanoic acid;
3-{[(4S)-3-Acetyl-1,3-thiazolinan-4-yl]carbonyl}amino-3-{4-[(3,5-
dichloroisonicotinoyl)amino]phenyl}propanoic acid;
3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-{[(2S)-1-[(3,5-
35 35 dichlorophenyl)sulphonyl]tetrahydro-1-H-pyrrol-2-yl]carbonyl}-
amino}propanoic acid;
(2RS,3RS)-3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-{[(2S)-1-[(3,5-
dichlorophenyl)sulphonyl]tetrahydro-1-H-pyrrol-2-yl]carbonyl]amino}-2-
40 40 hydroxypropanoic acid;
3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-{[(2-[(2,5-
30 30 dimethoxyphenyl)thio]-3-pyridinyl]carbonyl)amino}propanoic acid;
and the salts, solvates, hydrates and N-oxides thereof.

45 45 Compounds according to the invention are potent and selective inhibitors of $\alpha 4$ integrins. The ability of the compounds to act in this way may be simply
35 35 determined by employing tests such as those described in the Examples
hereinafter.

10

The compounds are of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role and the invention extends to such a use and to the use of the compounds for the manufacture of a medicament for treating such diseases or disorders.

15

Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

20

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

30

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

35

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and

45

50

10

preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

15

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

15

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

20

10 The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

25

15 20 In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

30

25 30 For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

35

40 45 The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by 35 instructions for administration.

50

55

10

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 5 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg 15 for nasal administration or administration by inhalation or insufflation.

15

20

10 The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols Ar¹, Alk^a, L¹, Ar², R¹, R^a, R^{a'} and R when used in the formulae depicted are to be understood to represent those groups described above in relation 15 to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard 20 practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups. For 25 convenience the processes described below all refer to a preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formula (2).

25

30

35

40

Thus according to a further aspect of the invention, a compound of formula 30 (1) in which R is a -CO₂H group may be obtained by hydrolysis of an ester of formula (3):

45



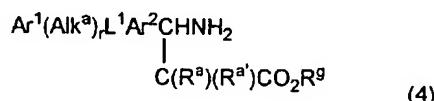
50

35 where R^g is an alkyl group, for example a C₁-6alkyl group as described above.

55

10 The hydrolysis may be performed using either an acid or a base depending on the nature of R⁹, for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium or potassium hydroxide optionally in
 5 an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient
 15 temperature. Where desired, mixtures of such solvents may be used.

10 20 Esters of formula (3) in which R¹ is a -NHCOR³ group may be prepared by coupling an amine of formula (4):



15 25 or a salt thereof with an acid R³CO₂H or an active derivative thereof. Active derivatives of acids include anhydrides, esters and halides.

30 The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in 20 a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around -30°C to around 35 ambient temperature, optionally in the presence of a base, e.g. an organic 35 base such as an amine, e.g. triethylamine, pyridine, or dimethyl- 40 aminopyridine, or a cyclic amine, such as N-methylmorpholine.

45 Where an acid R³CO₂H is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide 30 such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate,

for example ethylchloroformate, prior to reaction with the amine of formula (4).

10

Similar reaction conditions and reagents may be used to generate an intermediate ester of formula (3) in which R¹ is a -CONHR³ group, from an amine R³NH₂ or a salt thereof, and an acid Ar¹(Alk^a)L¹Ar²CH(CO₂H)C(R^a)(R^a)CO₂R⁹ or an active derivative thereof. Equally, similar reaction conditions and reagents may be used to obtain an ester of formula (3) in which R¹ is a -NHC(O)OR³ group from an amine of formula (4) and an appropriate chloroformate CICO₂R³.

15

10 Esters of formula (3) in which R¹ is a -NHCSR³ or -CSNHR³ group may be prepared by treating a corresponding ester in which R¹ is a -NHCOR³ or -CONHR³ group with a thiation reagent, such as Lawesson's Reagent, in 15 an anhydrous solvent, for example a cyclic ether such as tetrahydrofuran, 20 at an elevated temperature such as the reflux temperature.

25

20 This reaction may not be particularly suitable with starting materials in 30 which other carbonyl groups are present, for example in Ar¹, Ar² and/or R³, 35 and which might undesirably participate in the reaction. To avoid this the 40 reaction with the thiation reagent may be performed earlier in the synthesis of the compound of the invention with an intermediate in which other 45 carbonyl groups are absent and any required carbonyl groups then subsequently introduced by for example acylation as generally described 50 hereinafter.

40

Intermediate esters of formula (3) in which R¹ is a -NHCONHR³ or -NHCSNHR³ group may be prepared from the corresponding amine of 45 formula (4) by reaction with an isocyanate R³NCO or isothiocyanate 50 R³NCS. The reaction may be performed in a solvent such as acetonitrile or an ether at an elevated temperature, e.g. the reflux temperature.

45

45 Amines of formula (4) may also be used to obtain intermediate esters of 50 formula (3) in which R¹ is a -NHSO₂R³ group by reaction with a reagent 55 R³SO₂L⁶ (where L⁶ is a leaving group such as a halogen atom, e.g. a bromine, iodine or chlorine atom) in the presence of a base, for example an

50

55

inorganic base such as sodium hydride, in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide, at for example ambient temperature.

10

15

5 Intermediate esters of formula (3) in which R¹ is a -NHR³ group may be prepared by coupling an amine of formula (4) with a reagent R³X² in which X² is a leaving atom or group such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

20

25

10 The coupling reaction may be carried out using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an alcohol, e.g. methanol or ethanol, at a temperature from around ambient to the reflux temperature, optionally in the presence of a base such as an amine, e.g. triethylamine or N,N-diisopropylethylamine, or a cyclic amine, such as N-methylmorpholine or pyridine.

30

35

15 The intermediate amines of formula (4) may also be used to obtain esters of formula (3) in which R¹ is a -NHSO₂NHR³ group by reaction with a sulphamide R³NHSO₂NH₂ in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

40

45

20 In a further example compounds of the invention may be obtained from resin linked (e.g. Wang resin) amino acids e.g. suitably N-protected e.g. fluorenylmethoxycarbonyl protected aryl amino acids. Resin linked amines of formula (4) (R⁹ represents the resin linker) may be obtained for example by reduction of the nitro [-NO₂] group of suitable resin linked amino acids e.g. nitroaryl amino acids with for example a tin reagent e.g. stannous chloride in a solvent such as an amide e.g. a substituted amide such as dimethylformamide at for example ambient temperature, followed by reaction of the newly generated amino (-NH₂) group with for example an acid chloride Ar¹(Alk^a)_rCOCl or an isocyanate Ar¹(Alk^a)_rNCO optionally in the presence of an organic base e.g. an amine such as diisopropylethylamine in a solvent such as a halogenated hydrocarbon e.g. dichloro-

50

10

methane, at for example ambient temperature, followed by N-deprotection with for example an organic amine e.g. piperidine in a solvent such as an amide e.g. a substituted amide such as dimethylformamide. Resin linked compounds of formula (3) may be obtained by reaction of resin linked compounds of formula (4) with for example an acid (R^3CO_2H), isocyanate (R^3NCO), isothiocyanate (R^3NCS), sulphonyl halide ($R^3SO_2L^6$) or halide (R^3X) as previously described for the preparation of esters of formula (3). Compounds of the invention may be obtained from resin-linked compounds of formula (3) by cleavage from the resin with for example an organic acid, e.g. trifluoroacetic acid in an organic solvent, for example a halogenated hydrocarbon e.g. dichloromethane.

20

25

The amines of formula (4) may be obtained from simpler, known compounds by one or more standard synthetic methods employing substitution, oxidation, reduction or cleavage reactions as described below and in the Examples hereinafter. Particular substitution approaches include conventional alkylation, arylation, heteroarylation, acylation, thioacetylation, halogenation, sulphonylation, nitration, formylation and coupling procedures, including for example those just described to obtain esters of formula (3). It will be appreciated that these methods may also be used to obtain or modify other compounds of formulae (1) and (2) where appropriate functional groups exist in these compounds. Additionally, although a number of the R^3 containing intermediates and the acid $Ar^1(Alk^a)_L^1Ar^2CH(CO_2H)C(R^a)(R^{a'})CO_2R^9$ for use in the coupling reactions described above are known, others can be derived therefrom using these standard synthetic methods.

30

35

40

45

Thus compounds of the invention and intermediates thereto may be prepared by alkylation, arylation or heteroarylation. For example, compounds containing a $-L^2H$, or $-L^3H$ group (where L^2 and L^3 is each a linker atom or group) may be treated with reagent $(R^4)_uL^3Alk^3X^2$ or $R^{4a}X^2$ respectively in which X^2 is as previously described and R^{4a} is an alkyl group.

35 The reaction may be carried out in the presence of a base such as a carbonate, e.g. cesium or potassium carbonate, an alkoxide, e.g.

50

55

potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydro-furan.

10

15

20

25

30

35

40

45

50

55

- 5 In another example, compounds containing a -L²H or -L³H group as defined above may be functionalised by acylation or thioacylation, for example by reaction with one of the alkylating agents just described but in which X² is replaced by a -C(O)X³, C(S)X³, -N(R⁵)COX³ or -N(R⁵)C(S)X³ group in which X³ is a leaving atom or group as described for X². The reaction may be performed in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature. Alternatively, the acylation or thioacylation may be carried out under the same conditions with an acid or thioacid (for example one of the alkylating agents described above in which X² is replaced by a -CO₂H or -COSH group) in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively the acid may be reacted with a chloroformate, for example ethylchloroformate, prior to the desired acylation reaction
- 10 In a further example compounds may be obtained by sulphonylation of a compound containing an -OH group by reaction with one of the above alkylating agents but in which X² is replaced by a -S(O)Hal or -SO₂Hal group in which Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.
- 15 In another example, compounds containing a -L²H or -L³H group as defined above may be coupled with one of the alkylation agents just described but in which X² is replaced by an -OH group in a solvent such as

5

30

tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate.

10

In a further example, ester groups $-\text{CO}_2\text{R}^5$ or $-\text{CO}_2\text{Alk}^1$ in the compounds 5 may be converted to the corresponding acid $[-\text{CO}_2\text{H}]$ by acid- or base-catalysed hydrolysis depending on the nature of the groups R^5 or Alk^1 . Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an 15 aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

20

In a further example, $-\text{OR}^5$ or $-\text{OR}^{14}$ groups [where R^5 or R^{14} each represents an alkyl group such as methyl group] in compounds of formula 25 (1) may be cleaved to the corresponding alcohol $-\text{OH}$ by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C .

30

Alcohol $[-\text{OH}]$ groups may also be obtained by hydrogenation of a 20 corresponding $-\text{OCH}_2\text{R}^{14}$ group (where R^{14} is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or 25 hydrogen, from around ambient to the reflux temperature. In another example, $-\text{OH}$ groups may be generated from the corresponding ester $[-\text{CO}_2\text{Alk}^1$ or $\text{CO}_2\text{R}^5]$ or aldehyde $[-\text{CHO}]$ by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

40

In another example, alcohol $-\text{OH}$ groups in the compounds may be 30 converted to a corresponding $-\text{OR}^5$ group by coupling with a reagent R^5OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or 45 dimethylazodicarboxylate.

35 Aminosulphonyl amino $[-\text{NHSO}_2\text{NH}_2]$ groups in the compounds may be obtained, in another example, by reaction of a corresponding amine $[-\text{NH}_2]$

50

55

with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

10

5 In a further example amine (-NH₂) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient 10 temperature.

15

20 In a further example, amine [-NH₂] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient 15 temperature.

25

30 In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation using for example hydrogen in the presence of a metal catalyst, for example palladium on a support 20 such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

35

40 Aromatic halogen substituents in the compounds may be subjected to 25 halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl 30 group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

45

45 In another example, sulphur atoms in the compounds, for example when 35 present in a linker group L² or L³ may be oxidised to the corresponding sulphoxide or sulphone using an oxidising agent such as a peroxy acid.

50

55

5

32

10

e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

15

5 N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

20

10 Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

25

15 Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

30

20 Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

35

40 In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if 30 desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

45

45 Chromatography, recrystallisation and other conventional separation procedures may also be used with intermediates or final products where it 35 is desired to obtain a particular geometric isomer of the invention.

50

55

The following Examples illustrate the invention. All temperatures are in °C.
The following abbreviations are used:

10	NMM - N-methylmorpholine;	EtOAc - ethyl acetate;
	BOC - butoxycarbonyl;	Ar - aryl;
5	Me - methyl;	THF - tetrahydrofuran;
	DMSO - dimethylsulphoxide;	app - apparent
15	tBu - tertiary butyl;	HOBT - 1-hydroxybenzotriazole
	DIEA - Diisopropylethylamine;	MeOH - methanol
	EDC - 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide;	
10	EtOH - ethanol;	DMF - dimethylformamide;
	DCM - dichloromethane;	TFA - trifluoroacetic acid
20	All NMR's were obtained at 300MHz.	

25 15 **INTERMEDIATE 1**

3-Amino-3-(4-nitrophenyl)propanoic acid

To a hot solution of sodium ethoxide prepared from sodium (9.33g, 405mmol) and EtOH (330ml) was added a hot solution of hydroxylamine hydrochloride (28.17g, 405mmol) in water (18ml). A white precipitate was formed immediately. The mixture was cooled rapidly and the solid removed by filtration and washed with EtOH (40ml). The filtrate was then returned to the reaction flask and 4-nitrocinnamic acid (30g, 155mmol) was added. The mixture was heated to reflux overnight. The resulting mixture was cooled to 0° and the precipitate filtered off and the solid washed with EtOH (50ml), water (50ml) and finally EtOH (50ml) to give the title compound as a pale yellow solid (16g, 49%). δ H (D₂O) 8.31 (2H, d, \downarrow 8.7Hz, ArH), 7.69 (2H, d, \downarrow 8.7Hz, ArH), 4.81 (1H, app. dd, \downarrow 7.2, 7.1 CHNH₂), 2.94 (1H, dd, \downarrow 16.4, 7.7Hz, CHAH_B) and 2.86 (1H, dd, \downarrow 16.4 and 6.7Hz, CHAH_B); m/z (ES⁺, 60V) 211 (MH⁺).

30 **INTERMEDIATE 2**

Methyl-3-amino-3-(4-nitrophenyl)propanoate

Intermediate 1 (5g, 23.8mmol) was added to a solution of acetyl chloride (5ml) in MeOH (125ml). The resulting solution was stirred at room temperature overnight. The solvents were then removed *in vacuo* and the resulting solid was triturated with hot ether, collected by filtration and

5

34

10

washed with more ether to leave the title compound as a pale yellow powder (5.35g, 100%). δ H (D_2O) 8.32 (2H, d, \downarrow 8.9Hz, ArH), 8.75 (2H, d, \downarrow 8.9Hz, ArH), 4.90 (1H, dd, \downarrow 7.2, 6.9Hz, $CHNH_2$), 3.70 (3H, s, CO_2Me), 3.19 (1H, dd, \downarrow 17.1, 7.5 Hz, $CHAH_B$) and 3.09 (1H, dd, \downarrow 17.1, 6.6Hz, $CHAH_B$); m/z (ES $^+$, 60V) 225 (MH $^+$).

15

INTERMEDIATE 3

Methyl-3-(t-butylloxycarbonylamino)-3-(4-nitrophenyl)propanoate

20

A solution of di-*tert*-butyl dicarbonate (6.58ml, 28.6mmol) in THF (50ml) was added dropwise to a stirred solution of Intermediate 2 (5.35g, 23.8mmol) and sodium hydrogen carbonate (4.19g, 49.9mmol) in THF (100ml) and water (100ml). The mixture was stirred overnight at room temperature. The THF was then removed *in vacuo* and the aqueous residue extracted with EtOAc (75ml x 3). The combined organics were then washed with 10% aqueous citric acid (100ml) and brine (100ml), dried (Na_2SO_4) and evaporated under reduced pressure. The oil obtained was taken up in hot ether. The solution was then cooled to yield a white precipitate which was collected by filtration and washed with hexane to give the title compound (6.69g, 87%). δ H ($CDCl_3$) 8.20 (2H, d, \downarrow 8.7Hz, ArH), 7.47 (2H, d, \downarrow 8.7Hz, ArH), 5.71 (1H, br s, NH), 5.17 (1H, app. br s, $CHNH$), 3.63 (3H, s, CO_2Me), 2.87 (2H, app. br d \downarrow 5.6Hz, CH_2) and 1.42 (9H, s, tBu); m/z (ES $^+$, 60V) 347 (M $^+ + Na$).

25

30

INTERMEDIATE 4

Methyl-3-(4-aminophenyl)-3-(t-butylloxycarbonylamino)propanoate

35

40

45

50

A solution of Intermediate 3 (5.6g, 17.3mmol) and tin (II) chloride dihydrate (19.6g, 86.5mmol) in EtOH (100ml) was stirred overnight at room temperature. The EtOH was then removed *in vacuo* and the residue partitioned between DCM (250ml) and saturated aqueous $NaHCO_3$ (100ml). The resulting solid precipitate was removed by filtration and washed with copious DCM. The filtrate was then separated and the aqueous extracted with DCM (3 x 100ml). The combined organics were finally washed with brine (150ml), dried (Na_2SO_4) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO₂; DCM/EtOAc, 4:1) gave the title compound as a yellow oil (3.77g, 74%) δ H (DMSO-d⁶) 7.20 (1H, br d, \downarrow 8.5Hz, CONH), 6.93 (2H, d, \downarrow 8.4Hz,

55

5

35

10

ArH), 6.47 (2H, d, \downarrow 8.4Hz, ArH), 5.00 (2H, br s, NH₂), 4.74 (1H, m, ArCH), 3.52 (3H, s, CO₂Me), 2.67 (1H, dd, \downarrow 15.1, 8.4Hz, CH_AH_BCO₂Me), 2.56 (1H, dd, \downarrow 15.1, 6.8Hz, CH_AH_BCO₂Me) and 1.33 (9H, s, tBu). m/z (ES⁺, 60V) 295 (MH⁺).

5

INTERMEDIATE 5

15

Methyl-3-(tert-butyloxycarbonylamino)-3-(4-[(3,5-dichloroisonicotinoyl)amino]phenyl)propanoate

20

To a solution of Intermediate 4 (3.77g, 12.8mmol) in DCM (50ml) was added NMM (1.55ml, 14.1mmol) and a solution of 3,5-dichloroisonicotinyl chloride (prepared by the methods detailed in International Patent Application WO99/35163) (2.97g, 14.1mmol) in DCM (2ml). The reaction mixture was stirred for 3h and then diluted with DCM (200ml) and washed with water (2 x 75ml) and brine (75ml), dried (Na₂SO₄) and evaporated under reduced pressure. Purification of the residue by column chromatography (SiO₂; DCM /EtOAc, 4:1) gave the title compound as a white solid (4.7g, 81%). δ H (CDCl₃) 8.93 (1H, br s, NH), 8.51 (2H, s, ArCl₂H), 7.33 (2H, d, \downarrow 8.3Hz, ArH), 7.13 (2H, d, \downarrow 8.3Hz, ArH), 5.75 (1H, br s, NH_{Boc}), 4.90 (1H, app. dd, \downarrow 14.2, 6.0Hz, CHNH), 3.61 (3H, s, CO₂Me), 2.75 (2H, d, \downarrow 6.0Hz, CH₂) and 1.35 (9H, s tBu); m/z (ES⁺, 60V) 490 (M⁺⁺ Na).

25

INTERMEDIATE 6

30

Methyl-3-amino-3-(4-[(3,5-dichloroisonicotinoyl)amino]phenyl)propanoate trifluoroacetic acid salt

40

To a solution of Intermediate 5 (4.7g, 10.3mmol) in DCM (100ml) and water (0.5ml) was added TFA (1.59ml, 20.6mmol) dropwise. The solution was stirred at room temperature for 4h. The volatiles were then removed *in vacuo* and the resulting yellow oil triturated with hexane/ether (~1:2) to give a sticky semi-solid. A small amount of EtOAc was then added and the solution heated to produce a white solid. The solution was then cooled, filtered and the solid washed with ether to leave the title compound (4.9g, 100%) as a white solid. δ H (D₂O) 8.69 (2H, s, ArCl₂H), 7.72 (2H, d, \downarrow 8.4Hz, ArH), 7.59 (2H, d, \downarrow 8.4Hz, ArH), 4.91 (1H, dd, \downarrow 7.2, 7.2Hz, CH), 3.75 (3H, s, CO₂Me), 3.30 (1H, dd, \downarrow 16.9, 7.5Hz, CH_AH_B) and 3.21 (1H, dd, \downarrow 16.9, 7.0Hz, CH_AH_B); m/z (ES⁺, 60V) 368 (MH⁺).

45

50

55

INTERMEDIATE 7**N-(3,5-Dichlorobenzenesulphonyl)-L-proline methyl ester**

10 3,5-Dichlorobenzenesulphonyl chloride (5.0g, 20.36mmol) was added
5 portionwise over 30min to a solution of *L*-proline methyl ester hydrochloride
(3.69g, 22.4mmol) and DIEA (7.8ml, 44.8mmol) in DCM (100ml) at 0°. The
15 reaction mixture was stirred overnight at room temperature then
concentrated *in vacuo*. The residue was dissolved in EtOAc (100ml) and
washed with saturated aqueous NaHCO₃ (100ml), citric acid (10%, 100ml)
10 and saturated aqueous NaHCO₃ (100ml). The organic phase was dried
(MgSO₄) and concentrated *in vacuo*. Column chromatography (SiO₂,
EtOAc/hexane, 80:20) gave the title compound (3.77g). δH (CDCl₃) 7.8
20 (2H, d, J 2.0Hz, ArH), 7.5 (1H, d, J 2.0Hz, ArH), 4.4 (1H, m, CH α), 3.7 (3H,
s, CO₂Me), 3.4 (2H, m, CH₂N), 2.0 (4H, m, NCH₂CH₂CH₂); m/z (ES⁺,
15 70V), 338 (MH⁺).

25

INTERMEDIATE 8**N-(3,5-Dichlorobenzenesulphonyl)-L-proline**

30 Lithium hydroxide monohydrate (555mg, 13.24mmol) was added to
20 Intermediate 7 (3.73g, 11.03mmol) in THF (25ml) and water (25ml). The
mixture was stirred at room temperature overnight then concentrated *in
vacuo*. Water was added to the residue and the pH adjusted to pH1 with
35 1.0M HCl. The resulting precipitate was filtered off, washed with water and
dried to give the title compound as a white solid (3.48g). δH (CDCl₃) 7.8
25 (2H, s, ArH), 7.6 (1H, s, ArH), 4.4 (1H, m, CH α), 3.6 (1H, m, NCH_AH_B), 3.5
(1H, m, NCH_AH_B), 2.0 (4H, m, NCH₂CH₂CH₂); m/z (ES⁺, 70V) 324 (MH⁺).

40

INTERMEDIATE 9**Ethyl (2RS, 3RS)-3-azido-2-hydroxy-3-(4-nitrophenyl)propanoate**

30 A mixture of ethyl (2RS, 3RS)-3-(4-nitrophenyl)-2-oxirane carboxylate
[prepared by the method of Moyna, G., Williams, H. J., Scott, A. I., Synth.
45 Commun, (1996) 26, 2235-9] (2.5g, 10.5mmol) sodium azide (3.4g,
52.5mmol), ethyl formate (10ml) in EtOH/water (8:1, 50ml) was heated at
50° overnight. The mixture was diluted with EtOAc, washed with water
35 and brine, dried (Na₂SO₄) and evaporated *in vacuo*. Column
chromatography (SiO₂; MeOH/DCM, 1:99) gave the title compound as a
50

55

10

yellow oil (2.34g) (less polar regioisomer). δ H (CDCl₃) 8.24 (2H, d, \downarrow 8.8Hz, ArH), 7.55 (2H, d, \downarrow 8.9Hz, ArH), 5.02 (1H, d, \downarrow 3.7Hz, CHN₃), 4.57 (1H, dd, \downarrow 5.3, 3.7Hz, CHO_H), 4.25-4.14 (2H, m, CO₂CH₂), 3.15 (1H, d, \downarrow 5.5Hz, OH), 1.21 (3H, t, \downarrow 7.2Hz, CO₂CH₂CH₃). m/z (ES⁺, 70V) 253 (M⁺-N₂).

15

INTERMEDIATE 10**Ethyl (2RS, 3RS)-3-amino-3-(4-aminophenyl)-2-hydroxypropanoate**

20

A mixture of Intermediate 9 (1.38g, 4.93mmol) and palladium on charcoal (10%wt, Pd, 140mg) in EtOH (50ml) was stirred under a hydrogen atmosphere (balloon) at room temperature overnight. The catalyst was filtered off and the filtrate concentrated *in vacuo* to give the title compound as a yellow gum (1.10g) δ H (DMSO-d₆) 6.93 (2H, d, \downarrow 8.4Hz, ArH), 6.44 (2H, d, \downarrow 8.4Hz, ArH), 4.00 (2H, q, \downarrow 7.1Hz, CO₂CH₂CH₃), 4.00 (1H, CHNH₂), 3.82 (1H, d, \downarrow 6.0Hz, CHO_H), 1.12 (3H, t, \downarrow 7.1Hz, CO₂CH₂CH₃), 4.80 (2H, br s, ArNH₂), 3.30 (2H, v br s, CHNH₂), 1.90 (1H, v br s, OH); m/z (ES⁺, 70V) 208 (M⁺-NH₃).

25

30

INTERMEDIATE 11**3-(9-Fluorenylmethoxycarbonylamino)-3-(4-nitrophenyl)propanoic acid.**

35

A cold (0°) solution of 3-amino-3-(4-nitrophenyl)propanoic acid (3.2g, 15mmol) in 10% aqueous sodium carbonate (60ml) and 1,4-dioxan (30ml) was treated portion-wise with 9-fluorenylmethoxycarbonyl-N-hydroxysuccinimide (5.6g, 17mmol) in 1,4-dioxan (15ml) and the mixture stirred at room temperature for 12h. The mixture was poured into water (300ml) and the aqueous phase washed 3 times with ether. The aqueous layer was then acidified with solid citric acid and extracted into ether. The combined organic layers were dried (MgSO₄) and evaporated to a yellow oil then triturated from hexane and EtOAc to afford the title compound as a yellow solid (2.83g); m/z (ES⁺, 70V) 432 (MH⁺).

40

45

INTERMEDIATE 12**Resin bound 3-(9-Fluorenylmethoxycarbonylamino)-3-(4-aminophenyl)propanoic acid**

50

55

5

10

Wang resin (Advanced Chemtech, 2.5g, 0.8mmol/g, 2mmol equivalent) in a mixture of DMF (20ml) and DCM (20ml) was treated with 3-(9-fluorenylmethoxycarbonylamino)-3-(4-nitrophenyl)propanoic acid (2.6g, 6mmol), 4-dimethylaminopyridine (244mg, 2mmol) and 1,3-diisopropylcarbodiimide (940 μ l, 6mmol) and the mixture agitated under nitrogen at room temperature for 24h. The resin was filtered and washed with DMF and DCM. The resin was treated with a 1M solution of stannous chloride dihydrate in DMF (50ml) at room temperature for 8h then washed as before to give the title compound.

15

10

INTERMEDIATE 13

20

Resin bound 3-[4-[(3,5-dichloroisocotinoyl)amino]phenyl]-3-aminopropanoic acid

25

Intermediate 12 (3.3g, 0.28mmol/g, 0.9mmol equivalent) was treated with DIEA (1.6ml, 9mmol) and 3,5-dichloro-4-pyridinecarbonyl chloride (1.9g, 9mmol) in DCM (20ml) with agitation at room temperature for 12h. The resin was filtered and washed with DMF and DCM followed by treatment with a 20% solution of piperidine in DMF (40ml) for 40min at room temperature then filtered and washed as before to afford the title compound.

30

INTERMEDIATE 14

35

Resin bound 3-[4-[(2,6-dichlorobenzoyl)amino]phenyl]-3-aminopropanoic acid

Intermediate 14 was prepared in a similar manner to Intermediate 13 from Intermediate 12, using 2,6-dichlorobenzoylchloride for 8h.

40

EXAMPLE 1**Methyl-3-[(2-chloronicotinoyl)amino]-3-[4-[(3,5-dichloroisocotinyl)amino]phenyl]propanoate**

45

To a suspension of Intermediate 6 (600mg, 1.24mmol) in DCM (25ml) was added 2-chloronicotinic acid (195mg, 1.24mmol), NMM (287 μ l, 2.61mmol), HOBT (190mg, 1.37mmol) and EDC (267mg, 1.37mmol). The resulting solution was stirred overnight at room temperature and then diluted with DCM (100ml) and washed with saturated aqueous NaHCO₃ (50ml), water (50ml) and brine (50ml), dried (Na₂SO₄) and evaporated under reduced

50

55

pressure. The residue was then purified by column chromatography (SiO₂, DCM/MeOH, 95:5) to give the title compound as a creamy solid. δH (DMSO-d⁶) 9.18 (1H, d, \downarrow 8.4Hz, NH), 8.79 (2H, s, ArCl₂H), 8.46 (1H, dd, \downarrow 4.8, 1.8Hz, ArClH), 7.82 (1H, dd, \downarrow 7.5, 1.8Hz, ArClH), 7.62 (2H, d, \downarrow 8.5Hz, ArH), 7.49 (1H, dd, \downarrow 7.5, 4.8Hz, ArClH), 7.41 (2H, d, \downarrow 8.5Hz, ArH), 5.45-5.37 (1H, m, CH), 3.60 (3H, s, OMe) and 2.86 (2H, d, \downarrow 8.0Hz, CH₂); m/z (ES⁺, 60V) 507 (MH⁺).

15

EXAMPLE 2**10 3-[(2-Chloronicotinoyl)amino]-3-(4-[(3,5-dichloroisonicotinoyl)-amino]phenyl)propanoic acid**

20

The compound of Example 1 (340g, 0.67mmol) was dissolved in a mixture of THF (5ml) and water (5ml). Lithium hydroxide monohydrate (31mg, 0.74mmol) was added and the mixture stirred at room temperature for 3h.

25

15 The THF was removed under reduced pressure and the aqueous residue acidified with aqueous HCl (1M). The resulting white precipitate was collected by filtration and washed well with water. Freeze drying from a mixture of MeOH and water gave the title compound as a white solid (193mg, 58%). δH (DMSO-d⁶) 12.30 (1H, br s CO₂H), 10.91 (1H, s, NH),

30

20 9.12 (1H, d, \downarrow 8.2Hz, NH), 8.79 (1H, s, ArCl₂H), 8.46 (1H, dd, \downarrow 4.8, 1.9Hz, ArClH), 7.81 (1H, dd, \downarrow 7.5, 1.9Hz, ArClH), 7.61 (2H, d, \downarrow 8.5Hz, ArH), 7.49 (1H, dd, \downarrow 7.5, 4.8Hz, ArClH), 7.41 (2H, d, \downarrow 8.5Hz, ArH), 5.38-5.31 (1H, m, CH) and 2.84-2.69 (2H, m, CH₂); m/z (ES⁺, 60V) 493 (MH⁺).

35

25 EXAMPLE 3**Methyl-3-(3,5-dichloroisonicotinoyl)amino)-3-(4-[(3,5-dichloroisonicotinoyl)amino]phenyl)propanoate**

40

To a suspension of Intermediate 6 (600mg, 1.24mmol) in DCM (25ml) was added NMM (287μl, 2.61mmol) followed by 3,5-dichloroisonicotinoyl chloride (272mg, 1.36mmol). The mixture was stirred for 2h and then diluted with DCM (100ml) and washed with water (2 x 50ml) and brine (50ml), dried (Na₂SO₄) and evaporated under reduced pressure. The residual peach foam was purified by column chromatography (SiO₂, DCM/MeOH, 92:8) to give the title compound as a pale cream oil (629mg, 94%).

45

35 δH (CDCl₃) 9.01 (1H, s, NH), 8.41 (2H, s, ArCl₂H), 8.39 (2H, s, ArCl₂H), 7.73 (1H, d, \downarrow 8.2Hz, NH), 7.44 (2H, d, \downarrow 8.5Hz, ArH), 7.28 (2H, d, \downarrow 8.5Hz,

50

55

5

40

10

ArH), 5.49 (1H, dd, \downarrow 8.0, 6.4Hz, CH), 3.62 (3H, s, Me), 2.94 (1H, dd, \downarrow 16.1, 6.6Hz, CH_AH_B) and 2.86 (1H, dd, \downarrow 16.1, 6.2Hz, CH_AH_B); m/z (ES⁺, 60V) 241 (MH⁺).

20

5 EXAMPLE 4

3-[(3,5-Dichloroisonicotinoyl)amino]-3-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoic acid

The title compound was prepared by the method of Example 2 from the compound of Example 3 as a pale cream solid (356mg, 58%). δ H (DMSO d⁶) 10.92 (1H, s, NH), 9.41 (1H, d, \downarrow 8.1Hz, NH), 8.78 (2H, s, ArCl₂H), 8.68 (2H, s, ArH), 5.37 (1H, app. q, \downarrow 7.4Hz, CH) and 2.75 (2H, d, \downarrow 7.4Hz, CH₂); m/z (ES⁺, 60V) 527 (MH⁺).

15

EXAMPLE 5

Methyl-3-(4-[(3,5-dichloroisonicotinoyl)amino]phenyl)-3-[(2,6-dimethoxybenzoyl)amino]propanoate

To a suspension of Intermediate 6 (600mg, 1.24mmol) in DCM (25ml) was added NMM (287ml, 2.61mmol) and 2,6-dimethoxybenzoyl chloride (23mg, 1.36mmol). The reaction mixture was stirred for a further 2h and then diluted with DCM (100ml) and washed with water (2 x 100ml) and brine (1 x 100ml), dried (Na₂SO₄) and evaporated under reduced pressure. The resulting semi-solid was purified by column chromatography (SiO₂, DCM /MeOH, 92:8) to give the title compound as a pale cream oil (658mg, 100%). δ H (CDCl₃) 8.48 (2H, s, ArCl₂H), 8.38 (1H, s, NH), 7.55 (2H, d, \downarrow 8.6Hz, ArH), 7.39 (2H, d, \downarrow 8.6Hz, ArH), 7.28 (1H, t, \downarrow 8.4Hz, Ar(OMe)₂H), 6.91 (1H, d, \downarrow 8.6Hz, NH), 6.55 (2H, d, \downarrow 8.4Hz, Ar(OMe)₂H), 5.60-5.30 (1H, m, CH), 3.78 (6H, s, OMe x 2), 3.63 (3H, s, CO₂Me), 3.01 (1H, dd, \downarrow 16.0, 5.7Hz, CH_AH_B) and 2.93 (1H, dd, \downarrow 16.0, 5.7Hz, CH_AH_B); m/z (ES⁺, 60V) 532 (MH⁺).

30

EXAMPLE 6

3-[(4-[(3,5-Dichloroisonicotinoyl)amino]phenyl)-3-[(2,6-dimethoxybenzoyl)amino]propanoic acid

The title compound was prepared by the method of Example 2 from the compound of Example 5 as a white solid (270mg, 42%). δ H (DMSO-d⁶) 10.84 (1H, s, NH), 8.77 (2H, s, ArCl₂H), 8.50-8.40 (1H, m, NH), 7.58 (2H,

45

50

55

5

41

10

d, \downarrow 8.5Hz, ArH), 7.40 (2H, d, \downarrow 8.5Hz, ArH), 7.27 (1H, t, \downarrow 8.4Hz, Ar(OMe)₂H), 6.64 (2H, d, \downarrow 8.4Hz, Ar(OMe)₂H), 5.30 (1H, app. q, \downarrow 7.5Hz, CH), 3.10 (6H, s, OMe), 2.72 (1H, dd, \downarrow 15.4, 7.0Hz, CH_AH_B) and 2.65 (1H, dd, \downarrow 15.4, 7.2Hz, CH_AH_B); *m/z* (ES⁺, 60V) 518 (MH⁺).

15

5

EXAMPLE 7

20

Methyl-3-[4-[(dichloroisonicotinoyl)aminophenyl]-3-(4,6-dimethoxy-1,3,5-triaz-2-ylamino)propanoate

25

Intermediate 6 (1.0g, 2.07mmol) was partitioned between EtOAc (100ml) and saturated aqueous NaHCO₃ solution (100ml). The phases were thoroughly shaken and then separated and the aqueous layer extracted with EtOAc (2 x 100ml). The combined organic phases were dried (Na₂SO₄) and evaporated to leave the free amine. A solution of the amine (626mg, 1.70mmol) 2-chloro-4,6-dimethoxy-1,3,5-triazene (404mg, 2.30mmol) and NMM (233μl, 2.30mmol) in MeOH was stirred overnight at 60°. The MeOH was removed *in vacuo* and the residue partitioned between EtOAc (100ml) and saturated aqueous NaHCO₃ (100ml). The phases were separated and the aqueous layer extracted with EtOAc (2 x 75ml). The combined organics were then washed with 5% aqueous citric acid (50ml), saturated aqueous NaHCO₃ (50ml) and brine (50ml), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂, DCM/MeOH, 92:8) to give the *title compound* as a cream foam (370mg, 43%) δ H (CDCl₃) 9.29 (H, s, NH), 8.38 (2H, s, ArCl₂H), 7.54 (2H, d, \downarrow 8.5Hz, ArH), 7.28 (2H, d, \downarrow 8.5Hz, ArH), 6.81 (1H, d, \downarrow 8.4Hz, NH), 5.53 (1H, dd, \downarrow 6.7, 6.2Hz, CH), 3.85 (3H, s, OMe), 3.83 (3H, s, OMe), 3.59 (3H, s, CO₂Me), 2.96 (1H, dd, \downarrow 16.8, 6.7Hz, CH_AH_B) and 2.84 (1H, dd, \downarrow 16.8, 6.2Hz, CH_AH_B); *m/z* (ES⁺, 60V) 529 (M⁺ Na).

30

30

EXAMPLE 8

35

3-[4-[(3,5-Dichloroisonicotinoyl)aminophenyl]-3-(4,6-dimethoxy-1,3,5-triaz-2-ylamino)propanoic acid

45

The *title compound* was prepared by the method of Example 2 from the compound of Example 7 as a white powder (170mg, 47%). δ H (DMSO-d⁶) 10.89 (1H, s, NH), 8.48 (2H, s, ArCl₂H), 8.49 (1H, d, \downarrow 8.3Hz, NH), 7.58 (2H, d, \downarrow 8.5Hz, ArH), 7.40 (2H, d, \downarrow 8.5Hz, ArH), 5.36 (1H, ddd, \downarrow 8.6, 8.3,

50

55

5

42

6.4Hz, CH), 3.80 (6H, s, OMe), 2.87 (1H, dd, \downarrow 15.9, 8.6Hz, CH_AHB) and 2.70 (1H, dd, \downarrow 15.9, 6.0Hz, CH_AHB); *m/z* (ES⁺, 60V) 493. (MH⁺).

10

EXAMPLE 9**5 Methyl 3-[(3,5-dichloroisonicotinoyl)amino]phenyl]-3-[(6-(propylsulphonyl)-4-pyrimidinyl)amino]propanoate**

15

A mixture of Intermediate 6 (502mg, 1.00mmol) 4,6-bis(propylsulphonyl) pyrimidine (prepared from 4,6-dichloropyrimidine, propanethiol and sodium hydride in THF) (321mg, 1.10mmol) and DIEA (348 μ l, 2.00mmol) in 10 acetonitrile (3ml) was heated at 50° overnight. The mixture was diluted with DCM, washed with dilute HCl, dried (Na₂SO₄) and evaporated *in vacuo*. Column chromatography (SiO₂: MeOH/DCM, 6:94) gave the title compound as a white foam (344mg). δ H (DMSO-d⁶) 10.91 (1H, s, CONH), 8.77 (2H, s, Cl₂PyH), 8.70 (1H, d, \downarrow 7.9Hz, NH), 8.57 (1H, s, ArH), 7.61 (2H, d, \downarrow 8.6Hz, ArH), 7.40 (2H, d, \downarrow 8.5Hz, ArH), 7.12 (1H, s, ArH), 5.55 (1H, m, CHNH), 3.56 (3H, s, CO₂Me), 3.36-3.32 (2H, m, SO₂CH₂), 2.93-2.89 (2H, m, CH₂CO₂), 1.63-1.55 (2H, m, SO₂CH₂CH₂CH₃), 0.93 (3H, t, \downarrow 7.4Hz, SO₂CH₂CH₂CH₃); *m/z* (ES⁺, 70V) 552 (MH⁺).

20

20 EXAMPLE 10**3-[(4-(3,5-Dichloroisonicotinoyl)amino]phenyl)-3-[(6-(propylsulphonyl)-4-pyrimidinyl)amino]propanoic acid**

35

The title compound was prepared by the method of Example 2 from the compound of Example 9 as a white powder. δ H (DMSO-d⁶) 12.34 (1H, br s, CO₂H), 10.90 (1H, s, CONH), 8.77 (2H, s, Cl₂PyH), 8.70 (1H, d, \downarrow 7.9Hz, NH), 8.55 (1H, s, ArH), 7.60 (2H, d, \downarrow 8.5Hz, ArH), 7.39 (2H, d, \downarrow 8.5Hz, ArH), 7.12 (1H, s, ArH), 5.52 (1H, m, CHNH), 3.4 (2H, m, SO₂CH₂), 2.90-2.75(2H, m, CH₂CO₂), 1.63-1.55 (2H, m, SO₂CH₂CH₂), 0.93 (3H, t, \downarrow 7.4Hz, SO₂CH₂CH₂CH₃); *m/z* (ES⁺, 70V) 538 (MH⁺).

40

30

EXAMPLE 11**Methyl 3-[(4-chloro-6-methoxy-1,3,5-triazin-2-yl)amino]-3-[(3,5-dichloroisonicotinoyl)amino]phenyl]propanoate**

45

A solution of dichloromethoxy-1,3,5-triazine (396mg, 2.2mmol) in 35 acetonitrile (5ml) was added to a mixture of Intermediate 6 (1.004g, 2mmol) and diisopropylethylamine (732 μ l, 4.2mmol) in acetonitrile (5ml) at 0°.

50

55

5

10

After 30min the mixture was diluted with DCM, washed with dilute HCl, dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2 : EtOAc/hexane, 65:35) gave the title compound as a colourless gum (694mg). δH (DMSO-d₆, 300K) (2 rotameric species observed) 10.91 (1H, s, CONH), 9.16 (d, \downarrow 8.1Hz) and 9.08 (d, \downarrow 8.6Hz) together (1H, CHNH), 8.78 (2H, s, PyH), 7.60 (2H, d, \downarrow 8.6Hz, ArH), 7.40-7.37 (2H, m, ArH), 5.41-5.32 (1H, m, CHCH₂), 3.86 (3H, s, OMe), 3.56 (3H, s, OMe), 2.97 (1H, dd, \downarrow 16.1, 8.6Hz, CHAH_BCO₂), 2.87 (1H, m, CHAH_BCO₂); m/z (ES⁺, 70V) 511 (MH⁺).

15

20

EXAMPLE 12**Methyl 3-(4-[(3,5-dichloroisonicotinoyl)amino]phenyl)-3-(4-[2-hydroxyethylamino]-6-methoxy-1,3,5-triazin-2-yl)amino)propanoate**

25

A mixture of the compound of Example 11 (350mg, 0.683mmol), DIEA (119 μ l, 0.683mmol) and ethanolamine (4.5 μ l, 0.75mmol) in THF (10ml) was stirred at room temperature overnight. The mixture was diluted with DCM, washed with dilute HCl, dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2 , MeOH/DCM, 10:90) gave the title compound as a colourless glass (204mg). δH (DMSO-d₆) (rotameric species observed) 10.87 (1H, s, CONH), 8.77 (2H, s, PyH), 7.85-7.65 (1H, m, NH), 7.56 (2H, d, \downarrow 8.6Hz, ArH), 7.39 (2H, m, ArH), 7.10-6.85 (1H, m, NH), 5.38 (1H, m, ArCHNH), 4.61 (1H, m, OH), 3.73-3.69 (3H, m, OMe), 3.55 (3H, s, OMe), 3.44 (2H, br s, CH₂CH₂), 3.30 (CH₂CH₂, peak under HOD), 2.95 (1H, m, CHAH_BCO₂Me), 2.75 (1H, dd, CHAH_BCO₂Me); m/z (ES⁺, 70V) 536 ((MH⁺)).

30

35

EXAMPLE 13**3-(4-[(3,5-Dichloroisonicotinoyl)amino]phenyl)-3-(4-[2-hydroxyethylamino]-6-methoxy-1,3,5-triazin-2-yl)amine)propanoic acid**

40

45

30 The title compound was prepared by the method of Example 2 from the compound of Example 12 as a white solid. δH (DMSO-d₆, 390K) 10.40 (1H, br s, CONH), 8.66 (2H, s, Cl₂PyH), 7.55 (1H, br, NH), 7.52 (2H, br d, ArH), 7.41 (2H, br d, \downarrow 8.5Hz, ArH), 6.36 (1H, br m, NH), 5.40 (1H, br m, ArCHNH), 3.76 (3H, s, OMe), 3.52 (2H, t, \downarrow 6.1Hz, NHCH₂CH₂CH), 3.34 (2H, q, \downarrow 5.7Hz, NHCH₂CH₂CH), 2.3 (1H, br s, OH) from 300K spectrum 2.8-2.5 (2H, m, CH₂CO₂H); m/z (ES⁺, 70V), 522 (MH⁺).

50

55

EXAMPLE 14

10 **Methyl 3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]-3-[(2S)-1-
[(3,5-dichlorophenyl)sulphonyl]tetrahydro-1-H-pyrrol-2-
5 yl]carbonyl]amino]propanoate**

15 EDC (158mg, 0.825mmol) was added to a mixture of Intermediate 6 (37.7mg, 0.75mmol) Intermediate 8 (243mg, 0.75mmol) HOBT (111mg, 0.825mmol) and NMM (173 μ l, 1.58mmol) in DMF (5ml). The mixture was stirred at room temperature overnight then the solvent removed *in vacuo*.

10 The residue was dissolved in EtOAc and washed with dilute HCl, NaHCO₃ (aqueous), water and brine, dried (Na₂SO₄) and evaporated *in vacuo*. Column chromatography (SiO₂: MeOH/DCM, 5:95) gave the **title compound** as a white foam (402mg). δ H (DMSO-d⁶) (mixture of diastereoisomers) 10.90 (1H, s, CONH), 8.78 (2H, s, Cl₂PyH), 8.53 (1H, m, 20 CHNH), both diastereoisomers), 8.00 (t, \downarrow 1.9Hz) and 7.97 (t, \downarrow 1.9Hz) together (1H, Cl₂ArH), 7.84 (d, \downarrow 1.9Hz) and 7.78 (d, \downarrow 1.9Hz) together (2H, Cl₂ArH), 7.60 (d, \downarrow 8.6Hz) and 7.59 (d, \downarrow 8.6Hz) together (2H, ArH), 7.36 (d, \downarrow 8.6Hz) and 7.34 (d, \downarrow 8.6Hz) together (2H, ArH), 5.18 (1H, m, CHNH), 4.22-4.14 (1H, m, CH α), 3.57 (3H, s, CO₂Me), 3.45-3.35 (1H, m, NCH_AH_B), 30 3.30 (1H, NCH_AH_B), 2.95-2.75 (2H, m, CH₂CO₂Me), 1.95-1.60 (4H, m, NCH₂CH₂CH₂); m/z (ES⁺, 70V) 675 (MH⁺).

EXAMPLE 15

35 **3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(2S)-1-[(3,5-
25 dichlorophenyl)sulphonyl]tetrahydro-1-H-pyrrol-2-yl]carbonyl]amino]
35 propanoic acid**

40 The **title compound** was prepared by the method of Example 2 from the compound of Example 14 as a white solid δ H (DMSO-d⁶) (2 diastereoisomers) 12.3 (1H, br s, CO₂H), 10.89 (1H, s, CONH), 8.78 (2H, s, Cl₂PyH), 8.53 (d, \downarrow 8.1Hz) and 8.48 (d, \downarrow 8.1Hz) together (1H, CONH), 8.00 (t, \downarrow 1.9Hz) and 7.97 (t, \downarrow 1.9Hz) together (1H, ArH), 7.85 (d, \downarrow 1.8Hz) and 7.78 (d, \downarrow 1.8Hz) together (2H, ArH), 7.61-7.57 (2H, m, ArH), 7.37-7.32 (2H, m, ArH), 5.13 (1H, m, CHNH), 4.24-4.16 (1H, m, CH α), 3.45-3.35 (1H, m, CH_AH_BN), 3.25 (1H, CH_AH_BN), 2.81 (1H, dd, \downarrow 15.8, 7.5Hz, 45 CH_AH_BCO₂), 2.75-2.69 (1H, m, CH_AH_BCO₂), 1.9-1.6 (4H, m, CH₂CH₂CH₂N); m/z (ES⁺, 70V) 659 (MH⁺).

EXAMPLE 16**Ethyl (2RS, 3RS)-3-[4-[(3,5-dichloroisonicotinoyl)amino]phenyl]-3-[4-(3,5-dichloroisonicotinoyl)amino]-2-hydroxypropanoate**

5 A solution of 3,5-dichloroisonicotinoylchloride (269mg, 1.28mmol) in DCM (5ml) was added to a solution of Intermediate 10 (130mg, 0.58mmol) and NMM (140 μ l, 1.28mmol) in DCM (5ml). After 3.5h at room temperature the mixture was diluted with DCM and washed with dilute HCl and NaHCO₃ (aqueous), dried (Na₂SO₄) and evaporated *in vacuo*. Column chromatography (SiO₂; MeOH/DCM, 7:93) gave the title compound as a white solid (198mg). δ H (DMSO-d⁶) 10.90 (1H, s, CONHAr), 9.56 (1H, d, \downarrow 9.0Hz, CONHCH), 8.79 (2H, s, Cl₂PyH₂), 8.67 (2H, s, Cl₂PyH₂), 7.58 (2H, d, \downarrow 8.6Hz, ArH), 7.38 (2H, d, \downarrow 8.6Hz, ArH), 5.88 (1H, d, \downarrow 6.0Hz, OH), 5.35 (1H, dd, \downarrow 9.0, 5.8Hz, NHCH), 4.32 (1H, t, \downarrow 5.9Hz, CHOH), 4.15-4.08 (2H, m, CO₂CH₂CH₃), 1.22 (3H, t, \downarrow 7.1Hz, CO₂CH₂CH₃). m/z (ES⁺, 70V) 573 (MH⁺).

EXAMPLE 17**(2RS,3RS)-3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[4-(3,5-dichloroisonicotinoyl)amino]-2-hydroxypropanoic acid**

30 The title compound was prepared by the method of Example 2 from the compound of Example 16 as an off white solid. δ H (DMSO-d⁶) 12.8 (1H, v br s, CO₂H), 10.90 (1H, s, CONHAr), 9.54 (1H, d, \downarrow 8.8Hz, NHCH), 8.78 (2H, s, Cl₂PyH₂), 8.66 (2H, s, Cl₂PyH₂), 7.57 (2H, d, \downarrow 8.4Hz, ArH), 7.39 (2H, d, \downarrow 8.4Hz, ArH), 5.6 (1H, v br s, OH), 5.37 (1H, dd, \downarrow 8.7, 5.4Hz, NHCH), 4.26 (1H, d, \downarrow 5.3Hz, CHOH); m/z (ES⁺, 70V) 545 (MH⁺).

EXAMPLE 18**Ethyl (2RS, 3RS)-3-[4-aminophenyl]-3-[(2S)-1-[(3,5-dichlorophenyl)sulphonyl]tetrahydro-1-H-pyrrol-2-yl]carbonyl]amino]-2-hydroxypropanoate**

45 A mixture of Intermediate 10 (250mg, 1.12mmol), Intermediate 8 (363mg, 1.12mmol), HOBT (166mg, 1.23mmol), NMM (135 μ l, 1.23mmol) and EDC HCl (236mg, 1.23mmol) in DMF (5ml) and DCM (10ml) was stirred at room temperature for 3 days. The solvents were removed *in vacuo*. The residue was dissolved in DCM, washed with dilute HCl and NaHCO₃ (aqueous),

5

46

10

dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2 : MeOH/DCM, 5:95) gave the title compound as a yellow oil (129mg). δH (DMSO-d⁶) (mixture of diastereoisomers) 8.23 (1H, d, \downarrow 8.7Hz, CONH), 8.00 (t, \downarrow 1.9Hz) and 7.98 (t, \downarrow 1.9Hz) together (1H, Cl_2ArH), 7.85 (d, \downarrow 1.9Hz) and 7.79 (d, \downarrow 1.9Hz) together (2H, Cl_2ArH_2), 6.99 (d, \downarrow 8.4Hz) and 6.94 (d, \downarrow 8.4Hz) together (2H, ArH), 6.48-6.42 (2H, m, ArH), 5.05-4.93 (3H, m, $\text{CH}_\alpha+\text{NH}_2$), 5.67 (d, \downarrow 5.7Hz) and 5.62 (d, \downarrow 6.1Hz) together (1H, OH), 4.4-4.3 (1H, m, $\text{CH}_\alpha\text{NH}$), 4.27-4.19 (1H, m, $\text{CH}_\alpha\text{OH}$), 4.06-3.98 (2H, m, $\text{CO}_2\text{CH}_2\text{CH}_3$), 3.40-3.20 (2H, m, CH_2N), 1.9-01.55 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.15 (t, \downarrow 7.1Hz) and 1.14 (t, \downarrow 7.1Hz) together (3H, $\text{CO}_2\text{CH}_2\text{CH}_3$); m/z (ES⁺, 70V) 552 (MH⁺).

15

20

EXAMPLE 19

**Ethyl (2RS,3RS)-3-{4[(3,5-dichloroisonicotinoyl)amino]phenyl}-3-
{[(2S)-1-[(3,5-dichlorophenyl)sulphonyl]tetrahydro-1-H-pyrrol-2-
yl]carbonyl}amino-2-hydroxypropanoate**

25

30

35

40

45

A solution of 3,5-dichloroisonicotinoyl chloride (55mg, 0.259mmol) in DCM (2ml) was added to a solution of the compound of Example 18 (125mg, 0.236mmol) and NMM (28 μ l, 0.259mmol) in DCM (5ml). The mixture was stirred overnight at room temperature then diluted with DCM, washed with dilute HCl, dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography (SiO_2 : MeOH/DCM, 6:94) gave the title compound as a yellow foam (135mg). δH (DMSO-d⁶) (mixture of diastereoisomers) 10.88 (1H, s, CONH), 8.78 (2H, s, Cl_2PyH_2), 8.50 (1H, app. t, \downarrow 9.1Hz, CONH), 8.01 (t, \downarrow 1.9Hz) and 7.97 (t, \downarrow 1.9Hz) together (1H, Cl_2ArH), 7.84 (d, \downarrow 1.9Hz) and 7.77 (d, \downarrow 1.9Hz) together (2H, Cl_2ArH_2), 7.58 (d, \downarrow 8.6Hz) and 7.55 (d, \downarrow 8.5Hz) together (2H, ArH), 7.35 (d, \downarrow 8.6Hz) and 7.30 (d, \downarrow 8.6Hz) together (2H, ArH), 5.89 (d, \downarrow 5.9Hz) and 5.84 (d, \downarrow 6.2Hz) together (1H, OH), 5.14-5.07 (1H, m, CH_α), 4.36-4.26 (2H, m, $\text{CH}_\alpha\text{NH} + \text{CH}_\alpha\text{OH}$), 4.11-4.04 (2H, m, CO_2CH_2), 3.45-3.20 (2H, m, CH_2N), 1.90-1.60 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.20 (t, \downarrow 7.1Hz) and 1.19 (t, \downarrow 7.1Hz) together (3H, $\text{CO}_2\text{CH}_2\text{CH}_3$).

EXAMPLE 20

50

55

10 **(2RS, 3RS)-3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-[(1(2S)-1-[3,5-dichlorophenyl)sulphonyl]tetrahydro-1H-pyrol-2-yi]carbonylamino)-2-hydroxypropanoic acid**

15 The title compound was prepared by the method of Example 2 from the compound of Example 19 as a pale brown solid. δ H (DMSO-d₆) (mixture of diastereoisomers) 12.7 (1H, br s, CO₂H), 10.87 (1H, s, CONH), 8.78 (2H, s, Cl₂PyH₂), 8.50 (d, \downarrow 8.9Hz) and 8.45 (d, \downarrow 8.8Hz) together (1H, CONH), 8.01 (t, \downarrow 1.9Hz) and 7.96 (t, \downarrow 1.9Hz) together (1H, Cl₂ArH), 7.86 (d, \downarrow 1.8Hz) and 7.78 (d, \downarrow 1.9Hz) together (2H, Cl₂ArH₂), 7.58-7.53 (2H, m ArH), 7.35 (d, \downarrow 8.7Hz) and 7.31 (d, \downarrow 8.6Hz) together (2H, ArH), 5.64 (1H, br m, OH), 5.16-5.09 (1H, m, CH α), 4.42-4.20 (2H, m, CH₂OH + CH₂NH), 3.50-3.20 (2H, m, CH₂N), 1.90-1.60 (4H, m, CH₂CH₂CH₂N); m/z (ES⁺, 70V) 677 (MH⁺).

20 15 **EXAMPLE 21**

25 **3-[(1(4S)-3-Acetyl-1,3-thiazolan-4-yi]carbonylamino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid**

30 Prepared from Intermediate 6 and N-Acetyl-D-thioproline by the methods described in Examples 18 and 2. δ H (DMSO-d₆, 390K) (mixture of diastereoisomers) 10.41 (1H, s, CONH), 8.69 (2H, s, Cl₂PyH₂), 7.99 (1H, br s, CONH), 7.59-7.57 (2H, m, ArH), 7.38-7.34 (2H, m, ArH), 5.26-5.21 (1H, m, CH α), 4.87-4.78 (2H, m, CH₂NH + NCH₂ArH₂S), 4.49-4.44 (1H, m, NCH₂ArH₂S), 3.35-3.30 (m) and 3.20-3.08 (m) and 2.87-2.64 (m) together (4H, m, CHCH₂S + CH₂CO₂H), 2.51 (s) and 2.50 (s) together (3H, COCH₃); m/z (ES⁺, 70V) 511 (MH⁺).

35 **EXAMPLE 22**

40 **3-[(1(4R)-3-Acetyl-1,3-thiazolan-4-yi]carbonylamino)-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid**

45 30 Prepared from intermediate 6 and N-acetyl-L-thioproline by the methods described in Examples 18 and 2. δ H (DMSO-d₆, 390K) (mixture of diastereoisomers) 10.41 (1H, s, CONH), 8.69 (2H, s, Cl₂PyH₂), 7.99 (1H, br s, CONH), 7.59-7.57 (2H, m, ArH), 7.38-7.34 (2H, m, ArH), 5.26-5.21 (1H, m, CH α), 4.87-4.78 (2H, m, CH₂NH + NCH₂ArH₂S), 4.49-4.44 (1H, m, NCH₂ArH₂S), 3.35-3.30 (m) and 3.20-3.08 (m) and 2.87-2.64 (m) together

5

48

(4H, m, $\text{CHCH}_2\text{S} + \text{CH}_2\text{CO}_2\text{H}$), 2.51 (s) and 2.50 (s) together (3H, COCH_3); m/z (ES $^+$, 70V) 511 (MH $^+$).

10

EXAMPLE 23**5 3-[4-[(2,6-Dichlorobenzoyl)amino]phenyl]-3-[(cyclohexyl)carbonyl]amino]propanoic acid**

15

To Intermediate 14 (130mg) was added DMF (0.5ml), DIEA in DMF (1M, 0.2ml), cyclohexanecarboxylic acid in DMF (1M, 0.3ml) and [O-(7-azabenzotriazol-1-yl)-1,3,3-tetramethyluronium]hexafluorophosphate in DMF (0.5M, 0.5ml). The solution was agitated at room temperature for 10h followed by filtration and multiple washes with DMF and DCM.

20

The resin was treated with a mixture of TFA, DCM and water (6:3:1) (3ml) for 3h with agitation and then filtered. The filtrate was evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford

15 the title compound (2mg)

25

HPLC-MS Retention time 3.9min; m/z (ES $^+$, 70V) 464 (MH $^+$).

HPLC-MS

30

HPLC-MS was performed on a Hewlett Packard 1100/MSD ES Single 20 Quadrupole system with diode array detector using a Luna C18(2) 50 x 4.6mm (3 μm particle size) column, running a gradient of 95% [20mM ammonium formate, pH 3.5], 5% [0.1% formic acid in acetonitrile] to 10% [20mM ammonium formate, pH 3.5], 90% [0.1% formic acid in acetonitrile] over 3 min, then maintaining the mobile phase at that ratio for a further 2 35 min. Flow rate 0.8ml/min.

40

The compounds of Examples 24 to 27 were prepared in a similar manner to the compound of Example 23, using Intermediate 14 and the carboxylic acid shown.

30

EXAMPLE 24**45 3-[4-[(2,6-Dichlorobenzoyl)amino]phenyl]-3-[(2-(3-pyridinyl)acetyl)amino]propanoic acid**

3-Pyridylacetic acid gave the title compound (4mg)

35 HPLC-MS Retention time 3.2min; m/z (ES $^+$, 70V) 472 (MH $^+$).

50

55

5

49

EXAMPLE 253-[4-[(2,6-Dichlorobenzoyl)amino]phenyl]-3-[(2-[2,5-

10

dimethoxyphenyl]thio]-3-pyridinyl]carbonyl]amino]propanoic acid2-(2,5-Dimethoxyphenylthio)-3-pyridine carboxylic acid gave the title
5 compound (5mg)HPLC-MS Retention time 3.9min; m/z (ES⁺, 70V) 626 (MH⁺).

15

EXAMPLE 263-[4-[(2,6-Dichlorobenzoyl)amino]phenyl]-3-[(3,3-10 dimethylbutanoyl]amino]propanoic acid

20

3,3-Dimethylbutanoic acid gave the title compound (2mg)HPLC-MS Retention time 3.9min; m/z (ES⁺, 70V) 451 (MH⁺).

25

The compounds of Examples 27 - 47 were prepared in a similar manner to
15 the compound of Example 23 using Intermediate 13 and the starting
material shown.**EXAMPLE 27**3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(2-[2,5-

30

dimethoxyphenyl]thio]-3-pyridinyl]carbonyl]amino]propanoic acid2-(2,5-dimethoxyphenylthio)-3-pyridine carboxylic acid gave the title
compound (4mg)HPLC-MS Retention time 3.7min; m/z (ES⁺, 70V) 627 (MH⁺).

35

EXAMPLE 283-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(2-chloro-3-
pyridinyl]carbonyl]amino]propanoic acid

40

2-Chloronicotinic acid gave the title compound (7mg)HPLC-MS Retention time 3.4min; m/z (ES⁺, 70V) 493 (MH⁺).

30

EXAMPLE 293-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(1-(4-
chlorophenyl)cyclopentyl]carbonyl]amino]propanoic acid

45

1-(4-Chlorophenyl)-1-cyclopentanecarboxylic acid gave the title compound

35 (3mg)

HPLC-MS Retention time 4.3min; m/z (ES⁺, 70V) 560 (MH⁺).

50

55

5

50

EXAMPLE 30

10

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(E)-3-phenyl-2-propenoyl]amino]propanoic acid

5 trans-Cinnamic acid gave the title compound (4mg)
HPLC-MS Retention time 3.8min; m/z (ES⁺, 70V) 484 (MH⁺).

15

EXAMPLE 31

20

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(4-phenylbutanoyl)amino]propanoic acid

4-Phenylbutanoic acid gave the title compound (3mg)
HPLC-MS Retention time 3.8min; m/z (ES⁺, 70V) 500 (MH⁺).

EXAMPLE 32

25

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(4-piperidinylcarbonyl)amino]propanoic acid

Isonipeptic acid gave the title compound (3mg)
HPLC-MS Retention time 2.9min; m/z (ES⁺, 70V) 465 (MH⁺).

30

EXAMPLE 33

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(4,6-dimethyl-2-oxo-2H-pyran-5-yl)carbonyl]amino]propanoic acid

35

Isodehydracetic acid gave the title compound (2mg)
HPLC-MS Retention time 3.4min; m/z (ES⁺, 70V) 504 (MH⁺).

25

EXAMPLE 34

40

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(cyclobutylcarbonyl)amino]propanoic acid

Cyclobutanecarboxylic acid gave the title compound (1mg)
HPLC-MS Retention time 3.6min; m/z (ES⁺, 70V) 436 (MH⁺).

45

EXAMPLE 35

50

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(cyclopropylcarbonyl)amino]propanoic acid

Cyclopropanecarboxylic acid gave the title compound (1mg)
HPLC-MS Retention time 3.5min; m/z (ES⁺, 70V) 422 (MH⁺).

55

EXAMPLE 38

10

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(3-methylcyclohexyl)carbonyl]amino]propanoic acid

5 3-Methyl-1-cyclohexanecarboxylic acid gave the title compound (2mg)
HPLC-MS Retention time 4.0min; m/z (ES $^+$, 70V) 478 (MH $^+$).

15

EXAMPLE 37

20

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(4-methylcyclohexyl)carbonyl]amino]propanoic acid

4-Methyl-1-cyclohexanecarboxylic acid gave the title compound (2mg)
HPLC-MS Retention time 4.0min; m/z (ES $^+$, 70V) 478 (MH $^+$).

EXAMPLE 38

25

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(3,3-dimethylbutanoyl)amino]propanoic acid

3,3-Dimethylbutanoic acid gave the title compound (5mg)
HPLC-MS Retention time 3.7min; m/z (ES $^+$, 70V) 452 (MH $^+$).

30

EXAMPLE 39**3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(5-(2-pyrazinyl)-1,3-thiazol-2-yl)carbonyl]amino]propanoic acid**

35

5-(2-Pyrazinyl)-2-thiazolylcarboxylic acid gave the title compound (2mg)
HPLC-MS Retention time 3.7min; m/z (ES $^+$, 70V) 453 (MH $^+$).

25

EXAMPLE 40

40

3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(1-methyl-5-nitro-1H-pyrazol-4-yl)carbonyl]amino]propanoic acid

1-Methyl-5-nitropyrazole-4-carboxylic acid gave the title compound (3mg)
HPLC-MS Retention time 3.6min; m/z (ES $^+$, 70V) 507 (MH $^+$).

45

EXAMPLE 41**3-[4-[(3,5-Dichloroisonicotinoyl)amino]phenyl]-3-[(4-methyl-1,2,3-thiadiazol-5-yl)carbonyl]amino]propanoic acid**

50

4-Methyl-1,2,3-thiadiazole-5-carboxylic acid gave the title compound (3mg)
HPLC-MS Retention time 3.6min; m/z (ES $^+$, 70V) 480 (MH $^+$).

55

EXAMPLE 42

3-(4-[(3,5-Dichloroisonicotinoyl)amino]phenyl)-3-[(2,1,3-benzoxadiazol-4-ylcarbonyl)amino]propanoic acid

5 Benzofurazan-5-carboxylic acid gave the title compound (3mg)
HPLC-MS Retention time 3.8min; m/z (ES $^+$, 70V) 500 (MH $^+$).

EXAMPLE 43

3-(4-[(3,5-Dichloroisonicotinoyl)amino]phenyl)-3-[(1-ethyl-3-methyl-

10 1H-pyrazol-5-yl)carbonyl]amino]propanoic acid

20 1-Ethyl-3-methyl-1H-pyrazole-5-carboxylic acid gave the title compound
(3mg)

HPLC-MS Retention time 3.6min; m/z (ES $^+$, 70V) 490 (MH $^+$).

EXAMPLE 44

3-(4-[(3,5-Dichloroisonicotinoyl)amino]phenyl)-3-[(1-phenylcyclopropyl)carbonyl]amino}propanoic acid

25 1-Phenyl-1-cyclopropanecarboxylic acid gave the title compound (4mg)
HPLC-MS Retention time 3.9min; m/z (ES $^+$, 70V) 498 (MH $^+$).

EXAMPLE 45

3-(4-[(3,5-Dichloroisonicotinoyl)amino]phenyl)-3-[(1-(4-chlorophenyl)cyclopentyl)carbonyl]amino]propanoic acid

35 1-(4-Chlorophenyl)-1-cyclopropanecarboxylic acid gave the title compound
(5mg)

HPLC-MS Retention time 4.1min; m/z (ES $^+$, 70V) 532(MH $^+$).

EXAMPLE 46

3-(4-[(3,5-Dichloroisonicotinoyl)amino]phenyl)-3-(propanoylamino)propanoic acid

40 Propanoic acid gave the title compound (2mg)

45 HPLC-MS Retention time 3.4min; m/z (ES $^+$, 70V) 410 (MH $^+$).

EXAMPLE 47

35 3-(4-[(3,5-Dichloroisonicotinoyl)amino]phenyl)-3-[(2-(3-pyridinyl)acetyl)amino]propanoic acid

3-Pyridylacetic acid gave the title compound (3mg)
HPLC-MS Retention time 3.1min; m/z (ES $^+$, 70V) 473 (MH $^+$).

10

EXAMPLE 48**5 3-[4-[(2,5-Dichlorophenyl)sulphonyl]amino]phenyl]-3-[(3,5-dichloroisonicotinoyl)amino]propanoic acid**

15

To Intermediate 12 (200mg) was added 2,5-dichlorobenzenesulfonyl chloride (98mg, 0.4mmol) in pyridine (10ml). The solution was agitated at room temperature for 12h followed by filtration and multiple washes with DMF and DCM. The resin was treated with a 20% solution of piperidine in DMF (10ml) for 30min at room temperature then filtered and washed as before.

20

To this resin was added DIEA (70 μ l, 0.4mmol) and 3,5-dichloroisonicotinoyl chloride (84 μ l, 0.4mmol) in DCM (10ml) and the solution agitated for 12h at room temperature followed by filtration and washes with DMF and DCM. The resin was treated with a 60% solution of TFA in DCM (5ml) for 3h with agitation at room temperature and then filtered. The filtrate was evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (3mg).

25

30 HPLC-MS Retention time 3.9min; m/z (ES $^+$, 70V) 563 (MH $^+$).

EXAMPLE 49**3-[4-[(3,5-Dichloroisonicotinoyl)aminophenyl]-3-[(3,4-dichloroanilino)carbonyl]amino]propanoic acid**

35

25 To Intermediate 12 (200mg) was added DIEA (70 μ l, 0.4mmol) and 3,5-dichlorononicotinoyl chloride (70 μ l, 0.4mmol) in DCM (10ml). The solution was agitated at room temperature for 12h followed by filtration and multiple washes with DMF and DCM. The resin was treated with a 20% solution of piperidine in DMF (10ml) for 30min at room temperature then filtered and washed as before.

40

30 To this resin was added DIEA (70 μ l, 0.4mmol) and 3,4-dichlorophenylisocyanate (75mg, 0.4mmol) in DCM (10ml) and the solution agitated for 12h at room temperature followed by filtration and washed with DMF and DCM.

45

35 The resin was treated with a 60% solution of TFA in DCM (5ml) for 3h with agitation at room temperature and then filtered. The filtrate was

50

10

evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (2mg)
HPLC-MS Retention time 4.7min; m/z (ES $^+$, 70V) 542 (MH $^+$).

15

5 **EXAMPLE 50**

3-(4-((3,4-Dichloroanilino)carbonyl)amino)phenyl)-3-((3,5-dichloroisonicotinoyl)amino)propanoic acid

20

To Intermediate 12 (200mg) was added DIEA (70 μ l, 0.4mmol) and 3,4-dichlorophenylisocyanate (75mg, 0.4mmol) in DCM (10ml) and the solution agitated for 12h at room temperature followed by filtration and washes with DMF and DCM. The resin was treated with a 20% solution of piperidine in DMF (10ml) for 30min at room temperature then filtered and washed as before.

25

To this resin was added DIEA (70 μ l, 0.4mmol) and 3,5-dichloronicotinoyl chloride (84 μ l, 0.4mmol) in DCM (10ml) and the solution agitated for 12h at room temperature followed by filtration and washes with DMF and DCM. The resin was treated with a 60% solution of TFA in DCM (5ml) for 3h with agitation at room temperature and then filtered. The filtrate was evaporated *in vacuo* to give the crude product which was purified by preparative HPLC to afford the title compound (5mg)
HPLC-MS Retention time 4.1min; m/z (ES $^+$, 70V) 542 (MH $^+$).

30

35

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC₅₀ value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

40

30

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

45

96 well NUNC plates were coated with F(ab)₂ fragment goat anti-human IgG Fc γ -specific antibody [Jackson Immuno Research 109-006-098: 100 μ l at 2 μ g/ml in 0.1M NaHCO₃, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing

50

55

(3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then performed at 37° for 30 min in a total volume of 200 μ l containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were fixed with 100 μ l MeOH for 10 minutes followed by another wash. 100 μ l 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100 μ l 50% (v/v) EtOH in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig
This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β -lympho blastoid cell-line JY was used in place of Jurkat cells. The IC₅₀ value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin
96 well tissue culture plates were coated with human plasma fibronectin (Sigma F0895) at 5 μ g/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100 μ l PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200 μ l containing 2.5×10^5 K562 cells, phorbol-12-myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

$\alpha_1\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic
96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2×10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200 μ l in the

5

56

10

presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and 100µl 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma 5 H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H₂O₂ (Sigma) and 50µg/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

15

20

α_{IIb}/β₃ -dependent human platelet aggregation

25

Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10⁸/ml in autologous plasma. Cuvettes contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; MgCl₂.H₂O 0.427; CaCl₂ 0.2; KCl 0.2; D-glucose 1.0; NaHCO₃ 1.0; 20 NaHPO₄.2H₂O 0.065). Aggregation was monitored following addition of 2.5µM ADP (Sigma) in the presence or absence of inhibitors.

30

35

In the above assays the preferred compounds of the invention generally have IC₅₀ values in the α₄β₁ and α₄β₇ assays of 1 µM and below. In the other assays featuring α integrins of other subgroups the same compounds had IC₅₀ values of 50µM and above thus demonstrating the potency and selectivity of their action against α₄ integrins.

40

45

50

55

Claims

5

10

15

20

25

30

35

40

45

50

55

CLAIMS

10

1. A compound of formula (1):

5 $Ar^1(Alk^a), L^1 Ar^2 CH(R^1) C(R^a)(R^{a'})R$ (1)

15

wherein

Ar¹ is an optionally substituted aromatic or heteroaromatic group;
 L¹ is a covalent bond or a linker atom or group selected from
 -CON(R²)- [where R² is a hydrogen atom or a C₁₋₃alkyl group],
 -SO₂N(R²)-, -C(O)O-, -N(R²)- or -O-;

20

Ar² is an optionally substituted phenylene or nitrogen-containing six-membered heteroarylene group;

25

R¹ is a group selected from -NHCOR³ [where R³ is an optionally substituted aliphatic, heteroaliphatic, cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, heteropolycycloaliphatic, aromatic or heteroaromatic group], -NHSO₂R³, -NHR³, -NHC(O)OR³, -NHCSR³, -NHCON(R³)(R^{3a}) [where R^{3a} is a hydrogen atom or a group R³ and R³ and R^{3a} are the same or different], -NHSO₂N(R³)(R^{3a}), -NHCSN(R³)(R^{3a}), -CON(R³)(R^{3a}) or -CSN(R³)(R^{3a});

30

R^a and R^{a'} which may be the same or different is each independently selected from a hydrogen or halogen atom or an optionally substituted straight or branched alkyl, alkenyl or alkynyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, or -(Alk^b)_mR^b group (in which Alk^b is a C₁₋₃alkylene chain, m is zero or the integer 1 and R^b is a -OH, -SH, -NO₂, -CN, -CO₂H, -CO₂R^c, (where R^c is an optionally substituted straight or branched C₁₋₆alkyl group), -SO₃H, -SOR^c, -SO₂R^c, -SO₃R^c, -OCO₂R^c, -C(O)H, -C(O)R^c, -OC(O)R^c, -C(S)R^c, -NR^dR^e [where R^d and R^e which may be the same or different is each a hydrogen atom or an optionally substituted straight or branched alkyl group], -C(O)N(R^d)(R^e), -OC(O)N(R^d)(R^e), -N(R^d)C(O)R^e, -CSN(R^d)(R^e), -N(R^d)C(S)R^e, -SO₂N(R^d)(R^e), -N(R^d)SO₂R^e, -N(R^d)CON(R^e)(R^f) [where R^f is a hydrogen atom or an optionally substituted straight or branched alkyl group], -N(R^d)C(S)N(R^e)(R^f) or -N(R^d)SO₂N(R^e)(R^f) group).

40

35 Alk^a is an optionally substituted aliphatic or heteroaliphatic chain;

55

5

58

10

r is zero or the integer 1;
R is a carboxylic acid (-CO₂H) or a derivative thereof;
and the salts, solvates, hydrates and N-oxides thereof.

15

- 5 2. A compound according to Claim 1 in which R is a -CO₂H group.
- 10 3. A compound according to any one of Claims 1 to 2 in which R^a is a hydrogen atom.
- 15 4. A compound according to any one of Claims 1 to 3 in which R^a is a hydrogen atom or a hydroxyl group.
- 20 5. A compound according to any one of Claims 1 to 4 in which (Alk^a)_rL¹ is a -CON(R²)- group.
- 25 6. A compound according to Claim 5 in which (Alk^a)_rL¹ is a -CONH- group.
- 30 7. A compound according to any one of Claims 1 to 6 in which Ar² is an optionally substituted 1,4-phenylene group.
- 35 8. A compound according to Claim 7 in which Ar² is a 1,4-phenylene group.
- 40 9. A compound according to any one of Claims 1 to 8 in which Ar¹ is an optionally substituted pyrimidinyl, pyridyl or phenyl group.
- 45 10. A compound according to Claim 9 in which Ar¹ is an optionally substituted pyridyl or phenyl group.
- 50 11. A compound according to Claim 10 in which Ar¹ is a 3,5-dichloropyridin-4-yl group.
- 55 12. A compound according to any one of Claims 1 to 11 in which R¹ is the group -NHCOR³ or -NHR³.

50

55

5

59

10 13. A compound according to Claim 12 in which R³ is an optionally substituted pyrrolidinyl, thiazolidinyl, phenyl, pyrimidinyl or 1,3,5-triazinyl group.

15 14. A compound which is:
3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-[(4-[2-hydroxyethyl-amino]-6-methoxy-1,3,5-triazin-2-yl)amine]propanoic acid;

20 3-{(3,5-Dichloroisonicotinoyl)amino]-3-[(4-[(3,5-dichloroisonicotinoyl)-amino]phenyl)propanoic acid;

25 10 3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-[(2,6-dimethoxybenzoyl)amino]propanoic acid;
3-[(4S)-3-Acetyl-1,3-thiazolinan-4-yl]carbonyl]amino-3-{4-[(3,5-dichloroisonicotinoyl)amino]phenyl}propanoic acid;

30 15 3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-[(2S)-1-[(3,5-dichlorophenyl)sulphonyl]tetrahydro-1H-pyrrrol-2-yl]carbonyl]amino]propanoic acid;
(2RS,3RS)-3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-[(2S)-1-[(3,5-dichlorophenyl)sulphonyl]tetrahydro-1H-pyrrrol-2-yl]carbonyl]amino-2-hydroxypropanoic acid;

35 20 3-{4-[(3,5-Dichloroisonicotinoyl)amino]phenyl}-3-[(2-[(2,5-dimethoxyphenyl)thio]-3-pyridinyl)carbonyl]amino]propanoic acid;
and the salts, solvates, hydrates and N-oxides thereof.

40 15. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

45

50

55

INTERNATIONAL SEARCH REPORT

Int. Jpnal Application No
PCT/GB 99/03986

A. CLASSIFICATION OF SUBJECT MATTER		
IPC 7 C07D213/79 A61K31/435 A61P37/00 A61P29/00 C07D401/12 C07D403/12		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC 7 C07D		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 64390 A (ARCHIBALD SARAH CATHERINE ;CELLTECH THERAPEUTICS LTD (GB); WARRELL) 16 December 1999 (1999-12-16) the whole document	1-15
E	WO 99 61465 A (ARCHIBALD SARAH CATHERINE ;CELLTECH THERAPEUTICS LTD (GB); WARRELL) 2 December 1999 (1999-12-02) the whole document	1-15
P, X	WO 99 10312 A (HOFFMANN LA ROCHE) 4 March 1999 (1999-03-04) the whole document	1-15
P, X	WO 99 43642 A (ARCHIBALD SARAH CATHERINE ;CELLTECH THERAPEUTICS LTD (GB); WARRELL) 2 September 1999 (1999-09-02) the whole document	1-15
-/-		-/-
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C.		<input checked="" type="checkbox"/> Patent family members are listed in annex.
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "S" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
13 April 2000		03.05.00
Name and mailing address of the ISA		Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl Fax: (+31-70) 340-3016		Stellmach, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/03986

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 99 37618 A (ARCHIBALD SARAH CATHERINE ;CELLTECH THERAPEUTICS LTD (GB); WARRELL) 29 July 1999 (1999-07-29) the whole document	1-15
X	WO 97 36859 A (RICO JOSEPH G ;SEARLE & CO (US); YU STELLA S (US); CHEN BARBARA B) 9 October 1997 (1997-10-09) * overlap of chemical formula * the whole document	1-15
Y	WO 98 00395 A (MERCK PATENT GMBH ;GOODMAN SIMON (DE); MAERZ JOACHIM (DE); RADDATZ) 8 January 1998 (1998-01-08) the whole document	1-15
Y	SAMANEN J ET AL: "VASCULAR INDICATIONS FOR INTEGRIN ALPHA V ANTAGONISTS" CURRENT PHARMACEUTICAL DESIGN, NL, BENTHAM SCIENCE PUBLISHERS, SCHIPHOL, vol. 3, 1997, pages 545-584, XP000872090 ISSN: 1381-6128 the whole document	1-15
P, X	LOBB, R.R. ET AL.: "Small molecule antagonists of alpha4 integrins: novel drugs for asthma" EXP. OPIN. INVEST. DRUGS, vol. 8, no. 7, July 1999 (1999-07), pages 935-945, XP000885957 the whole document	1-15

INTERNATIONAL SEARCH REPORTInternational application No.
PCT/GB 99/03986**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Present claims 1-11 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 12 e.g those compounds prepared in the examples 1-50 and closely related homologous compounds etc. see compounds mentioned in the description at pages 38-54 given partially in Formula 2, at page 19 *****

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. Application No.
PCT/GB 99/03986

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9964390	A	16-12-1999	NONE		
WO 9961465	A	02-12-1999	AU	3947599 A	13-12-1999
WO 9910312	A	04-03-1999	AU	9262098 A	16-03-1999
WO 9943642	A	02-09-1999	AU	3260399 A	15-09-1999
WO 9937618	A	29-07-1999	AU	2432099 A	09-08-1999
WO 9736859	A	09-10-1997	AU	2536097 A	22-10-1997
			CA	2250698 A	09-10-1997
			EP	0891325 A	20-01-1999
			US	5952381 A	14-09-1999
WO 9800395	A	08-01-1998	DE	19654483 A	02-01-1998
			AU	3343097 A	21-01-1998
			BR	9709953 A	10-08-1999
			CA	2259224 A	08-01-1998
			CZ	9804249 A	17-03-1999
			EP	0907637 A	14-04-1999
			NO	986090 A	23-12-1998
			PL	330915 A	07-06-1999
			SK	176898 A	07-05-1999